

FINAL REPORT

TASK FORCE ON CHEMICALS IN THE ENVIRONMENT
AND HUMAN REPRODUCTIVE PROBLEMS IN NEW BRUNSWICK

SUBMITTED TO THE DEPARTMENT OF HEALTH
PROVINCE OF NEW BRUNSWICK

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THE USE OF CHEMICALS IN THE ENVIRONMENT AND PATTERNS OF
REPRODUCTIVE OUTCOMES IN NEW BRUNSWICK

- Final Report of the Task Force on Chemicals in the
Environment and Human Reproductive Problems in New Brunswick

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Finally, we wish to acknowledge the New Brunswick Department of Health for having the interest in and commitment to public health to commission this extensive investigation.

SUMMARY

This is the final report of the Task Force on Chemicals in the Environment and Human Reproductive Problems in New Brunswick. The main purpose of this report is to address the 4th and 5th terms of reference:

To identify and examine any possible association between the use of chemicals in the environment and patterns of incidence of adverse human reproductive outcomes in New Brunswick, placing emphasis on the use of pesticides in the forest industry, but not to the exclusion of agricultural and domestic uses of chemicals.

To make recommendations regarding chemicals in the environment and their relationship to adverse human reproductive outcomes.

Background

All previous work is reviewed briefly in this final report.

Reproductive health statistics (neonatal deaths, postneonatal deaths, infant deaths, stillbirths, perinatal deaths, birth weight and sex ratio) were examined for various periods from as early as 1921 to as recently as 1981.

The rates of improvement in New Brunswick and Quebec were greater than seen in Nova Scotia and Canada as a whole, and all four jurisdictions now enjoy similar levels of reproductive health. Only stillbirths and perinatal mortality (which includes stillbirth) showed a consistent excess for New Brunswick.

Extensive literature reviews have focussed on neural tube defects which were documented to have a generally high prevalence in the Atlantic Provinces, facial clefts for which animal studies had shown some experimental evidence of relationship to phenoxyherbicide exposure, and renal agenesis because renal abnormalities have also been seen in animal studies. The toxicology of major pesticides used in forest spray programs was assessed, specifically fenitrothion, amniocarb, 2,4-D and 2,4,5-T. Access to information on Round-up[®] a herbicide recently introduced into forest management in Canada, was refused by the manufacturer Monsanto. This information is now being sought under the U.S. Freedom of Information Act, equivalent authority not being available in Canada.*

Patterns and trends of birth defects were examined for New Brunswick, and compared with up to 5 other provinces for which data were available from the Canadian Congenital Anomalies Surveillance System (CCASS). Despite generally lower rates of reporting, New Brunswick demonstrated consistently higher rates of neural tube defects than other provinces participating in CCASS. Counties within the Saint John River Basin were found to have generally higher anomaly rates than other counties, and were also more often associated with unusual seasonal peaks. Stillbirths analyses revealed an approximately annual cyclic pattern in seven adjacent counties, six of which are within the Saint John River Basin.

*Much of this information was received from the U.S. Environmental Protection Agency in March, 1985, and additional information is pending.

Four recommendations pertaining to reproduction outcomes were made in the second report, regarding:

- Maternal alpha fetoprotein screening for neural tube defects
- Vitamin supplementation and the possible prevention of neural tube defects
- Design of official health records
- Records linkage

Seven recommendations pertaining to toxicology assessments were made, regarding:

- Canadian criteria for the performance of toxicology studies
- Access to essential regulatory information by government appointed enquiries.
- Periodic regulatory review of licensed chemicals
- A product and environmental monitoring program
- An analytical chemist
- Use of primates in studies of teratogenicity and reproduction toxicology
- A maximum allowable contaminant level of 2,4,5-T

It was apparent from the outset of Task Force activities that one could not address the 4th term of reference without having a data base from which to derive estimates of chemical exposure. Much of the first year of work was therefore directed at developing such a resource. The present report presents the results of subsequent analyses for association between potential chemical exposures and adverse human reproductive outcomes, as well as consequent interpretations, conclusions and recommendations.

Studies of Association

Three distinct types of study have been carried out: geographic correlation analyses, analyses for temporal association, and case control studies. While complementary, these distinct approaches are not of equal merit in assessing possible relationships.

Geographic correlation analyses address the question of whether there is any evidence of association within counties between the amount of exposure and the frequency of birth defect occurrence by major subcategories across all calendar quarters during the study period.

Analyses for temporal association have been undertaken in two ways. First, the correlation analyses have been carried out at four quarterly lag intervals, which address the potential for delay between exposure and outcome taking into account the time required for fetal development, as well as possible delays between chemical application and actual exposures. The second approach involved comparisons of mean rates of occurrence in each county for the outcomes of interest when spraying took place with the corresponding rate in the subsequent three quarters (and at all quarterly lag intervals from 0 to 3).

Several case control studies were carried out. A case control study starts with identification of persons with disease (e.g. a birth defect subcategory) and a suitable reference group of persons without disease. The relationship of exposure to disease, if any exists, is judged by comparing the

case and control groups with regard to the exposure measure. The strength of such association in our studies is assessed by the magnitude and statistical significance of a standardized risk ratio.

Greatest importance should be accorded to the findings of the case control studies because only these studies utilize information on the estimated exposure for individuals. By contrast, the other methods used (lagged correlations and comparisons of mean rates), utilize aggregate data for counties and time periods. Such studies are inherently incapable of assuring us that an elevated frequency of outcome, associated with an elevated degree of exposure will be found true of individuals with that outcome. Nonetheless these aggregate approaches provide useful additional information.

Estimation of Chemical Exposures

The development of the chemical data base was described in the Second Report, and further elaborated in the present report. Two main issues are addressed: data on agricultural pesticide use, and the determination of exposure indices (for both forestry and agricultural chemicals). In addition, our efforts to obtain information on chemicals for home and garden use are documented.

Satisfactory data were found to exist for the Task Force to examine possible associations between adverse reproductive outcomes and forestry insecticides. Adequate data on forestry herbicides was available only since about 1980. Due to the serious lack of adequate data on agricultural chemical

usage, the Task Force relied on Soil Capability maps (taking into account the agricultural spray season) to serve as a basis for an Agricultural Chemical Exposure Opportunity Index. The lack of crop production statistics for non-census years made it impossible for the Task Force to examine, by way of correlation analysis and comparison of mean rates, county level association between the ACEO Index and reproductive outcomes. Case control studies were however feasible with this index, permitting assessment of association at an individual level. All three types of study were possible for specific categories for forestry pesticides. Data on home and garden pesticides were inadequate for any type of analysis although this could represent the most significant direct exposure of all categories considered.

An index of individual exposure was required in the case-control studies for each case and control that fell within the risk window. The "risk window" is defined as the critical period of organogenesis or fetal development during which a teratogenic effect could plausibly occur as a result of a (teratogenic) chemical exposure. The forestry maps discussed in the Second Report (pages 213-215) were used to calculate fenitrothion, aminocarb and phenoxyherbicide potential exposures. The Canada Land Inventory Soil Capability for Agriculture maps were used to calculate the ACEO Index. Exposure was calculated as follows:

1. For each case or control with potential exposure during a risk window, the mother's residence (town, city, etc.) as stated on the infant's birth certificate was determined and located on the appropriate map.

2. A transparent circle (a template) with a radius equivalent to 5 kilometres was placed on the map and the centre of this circle was aligned with the residence as defined in 1 above. The circle, which represents an area of approximately 78.5 square kilometers, contained 100 dots and each dot was so positioned so that is represented 1% of the area of the circle.

3. Keeping within the boundary of the circle, potential exposure to forest insecticide (fenitrothion, aminocarb) was quantified by counting the number of dots which superimposed the area of interest on the map. If none of the area of the template superimposed the area of the map depicting insecticide spray, then the potential exposure was represented by 0% (no dots) whereas if half of the 5 kilometre radius circle superimposed a spray area, then the potential exposure was 50% (50 dots in the circle). Determination of the ACEO Index was accomplished in a similar manner. Because of the imprecise areas on the map depicting phenoxy herbicide spray areas, only a plus (+) or minus (-) score was assigned for this group of chemicals.

Assessment of Evidence

Significantly elevated correlation coefficients were scrutinized for robustness and embryological plausibility. Robustness was judged to be adequate if the correlation coefficient remained elevated after the deletion of a few data points. Embryological plausibility was accorded only to those coefficients observed to occur at intervals consistent with recognized periods of fetal organ developments. Failure to meet these criteria led to rejection of some coefficients.

The results of correlation analysis and comparison of mean rates across intervals were compared. Evidence of association was considered consistent, if derived from both these approaches. However, if evidence from one approach failed to support evidence from the other, less importance would be attached to the finding. Not all studies of association were possible using both these aggregate approaches (neither were possible in reference to the ACEO Index). Finally, if evidence was obtained from case control study, this would be taken as the most reliable and valid type of evidence.

Association between an outcome and a given exposure may be causal or non-casual. To assess the likelihood of an association being the result of a cause and effect relationship, a series of criteria were applied: time relationship, biological plausibility, biological gradient, consistency, repeatability, strength, analogies, specificity and experimental evidence.

Limitations of this research are discussed in some detail, including the hypothesis, the absence of alternate hypotheses, availability of data, measurement problems, and potential biases at various stages of the research process.

Conclusions

Conclusions focus on the adequacy of chemical information, the results of studies of association and causal inference.

Chemical Information: Information on the use of chemicals in forestry is of much better quality than that available for agriculture. While the agricultural industry is more complex, and has many more individual chemical

users, the fact remains that the variety of chemicals used in agriculture is greater than in forestry and this industry poses greater potential for direct and indirect human exposure and improper use. Despite the complexity, adequate health and environmental monitoring requires development of post marketing surveillance of chemical use in agriculture.

The problem of access to information has been encountered at the federal level. Our current national policies and mechanisms are not sufficient to provide access even to a government appointed enquiry without agreement from the manufacturer. Information from Monsanto, the manufacturer of Roundup[®], was sought in the United States under the U.S. Freedom of Information Act.

Associations and Causal Inference: An association was found between the Agriculture Chemical Exposure Opportunity Index and the combined category of "major anomalies". However, this association lacks good evidence of a biological gradient, strength and specificity. The association is considered biologically plausible in view of compatible experimental and epidemiological evidence.

An association was found between the Agricultural Chemical Exposure Opportunity Index and spina bifida without hydrocephalus. However no such association was detected in reference to the combined category "all spina bifida" - a finding which detracts from the plausibility of this association. The ACEO index itself, while based on our extrapolation from land use and recommended chemical usage, might nonetheless represent some non-chemical characteristic of agricultural land use. The case for underlying causal phenomena clearly must be further investigated in New Brunswick, given the public health importance of neural tube defects.

Stillbirths were found to be significantly associated with exposure to the ACEO Index during the second trimester of pregnancy. This association shows some evidence of an exposure response gradient, but cannot be considered very specific (because neither the ACEO Index nor stillbirth are discrete entities). Consistency is gained from previous evidence of cyclic patterns of stillbirth within the Saint John River Basin - a prime agricultural area - and somewhat higher stillbirth rates provincially than seen in Canada or adjacent Quebec and Nova Scotia. Clearly there is a need to explore this association further.

No acceptable evidence of association was found between any of the forestry pesticide studies and any outcome category with the possible exception of renal agenesis in association with exposure to fenitrothion in the first trimester. This is raised in view of a statistically significant elevated risk in the lower of 2 exposure categories in only one of 2 case control studies. Although it gains no support from correlation analysis and comparisons between mean rates, an underlying association might fail to be detected due to small numbers. There is insufficient evidence here of a causal association and even the existence of a non-causal association may be seriously questioned.

Recommendations

These are presented in the following section.

RECOMMENDATIONS

1. Confirmation of Earlier Recommendations

The Task Force confirms the recommendations laid out in the Second Report with one amendment.

The amendment applies to recommendation 2.3 which refers to the Design and Management of Official Records. Sub-recommendation 2.3a should now read:

"That all obstetrical records should include a question on the level of schooling and occupation of the parents."

2. Information on Chemicals

2.1 The Task Force urges the New Brunswick government to continue development of information on agricultural chemical use in the province, so that the capability for post-marketing epidemiological surveillance and investigation will be enhanced. This means the inclusion of information on actual patterns (purpose, time, place, person, frequency, concentration and types) of chemical storage, use and disposal. The goal should be no less than the maintenance of an information system that compares with that already available for chemicals used in the forestry industry.

2.2 While considering current information on chemical use in forestry to be far superior to that which exists for agricultural chemical use, the Task Force recommends not only the maintenance of current information practices but wishes to encourage this industry to undertake further developments. While the collection and

consolidation of existing information has made our current studies possible, for other models of exposure and hypothetical outcomes (e.g., cumulative or interactive exposures and cancer) a computerized data base should make continued and comprehensive epidemiological surveillance a routine objective.

- 2.3 The Task Force considers that it is in the public interest to restate its earlier recommendation (Second Report 2.6) concerning Access to Essential Regulatory Information by Government Appointed Inquiries:

"The Task Force experienced considerable difficulty obtaining access to toxicologic evidence provided by pesticide manufacturers to Agriculture Canada, and in one instance was denied access to this information. The Task Force, therefore, recommends that the Government of New Brunswick encourage the Government of Canada, through legislation, to ensure that such information is available to any government appointed enquiry."

- 2.4 The Task Force recommends that there be a concerted effort by all levels of government to increase public knowledge about health and safety aspects of chemicals used in our environment, and to increase the level of personal responsibility and accountability among chemical users. Specifically, this means greater attention to packaging and labelling, public education programs, and increased requirements for the documentation of actual chemical use.

3. Associations with Adverse Reproductive Outcomes

3.1 It is very clear that, although there is no evidence that New Brunswick is at greater overall risk of birth defects generally, the birth prevalence of neural tube defects is substantially higher than most other areas of Canada. It is recognized that this pattern is shared by Atlantic Canada generally.

The Task Force, therefore, recommends that the Government of New Brunswick should recognize the occurrence of neural tube defects as a regional priority for research and service development. Future research should be directed across a broader range of hypotheses than that of environmental chemical exposure.

3.2 Having identified the need for a broad range of research, the fact remains that an association has been demonstrated by the Task Force between neural tube defects and potential agricultural chemical exposure, which appears to be concentrated within the Saint John River Basin and northern New Brunswick counties and in the subcategory of spina bifida without hydrocephalus.

While there is insufficient evidence to judge whether this is a causal relationship, clearly this possibility must be recognized. It is therefore recommended that research into neural tube defects in the context of the agricultural environment be given a high priority by the New Brunswick government, including both chemical and non-chemical hypotheses.

3.3 The Task Force has also identified an association between second trimester "exposure" to the ACEO Index and subsequent occurrence of

stillbirth. While this is a weak association, it is biologically plausible and there is some suggestion of an exposure response gradient. In view of this finding and because of an approximately annual cycle of stillbirths observed mainly within the Saint John River Basin and the fact that New Brunswick demonstrates a small but consistent excess of stillbirths when compared with Canada and adjacent provinces, there is a good case for continued investigation into this problem in reference to the agricultural environment.

- 3.4 It is the view of the Task Force that current epidemiological resources within New Brunswick are insufficient to meet the growing need for adequate health surveillance and investigation.

The Task Force recommends that a full time research epidemiologist be employed by New Brunswick, with a suitable academic appointment and terms of reference which relate clearly to provincial health issues (e.g., cancer, birth defects, occupational and environmental health).

4. Atlantic Canada Studies

Because the issues identified in this report are not unique to New Brunswick and have relevance to the Atlantic region generally, the Task Force recommends that where such issues are jointly identified (e.g. neural tube defects, data base development, environmental health) there should be an efficient pooling of expertise and resources in order to enhance the effectiveness and efficiency of research and service programs.

A. INTRODUCTION

The Task Force on Chemicals in the Environment and Human Reproductive Problems in New Brunswick was established late in 1982. Three documents have been prepared in advance of this final report: an Interim Report of April 29, 1983, a Supplementary Report on Aminocarb of May 16, 1983 (viewed as an extension of the Interim Report), and the Second Report of January 10, 1984. These reports, taken together with the contents of this final report, cover the original terms of reference to the extent that this is feasible from available data and other relevant information.

Terms of Reference

1. To assess the incidence* of adverse human reproduction outcomes (e.g. congenital abnormalities, perinatal mortality and spontaneous abortions) with emphasis on the period 1971-1981 in New Brunswick.
2. To compare the incidence of similar outcomes over the same period of emphasis in other Canadian jurisdictions.
3. To analyse intra-provincial variation in incidence in order to determine temporal and/or geographical clustering.
4. To identify and examine any possible association between the use of chemicals in the environment and patterns of incidence of adverse human reproductive outcomes in New Brunswick, placing emphasis on the use of pesticides in the forest industry, but not to the exclusion of agricultural and domestic uses of chemicals.

* For reasons outlined in the Second Report the strict definition of incidence cannot be applied to the available data. Instead, where original analyses of birth anomalies and stillbirths were carried out, the more correct term of "birth prevalence" is used.

5. To make recommendations regarding chemicals in the environment and their relationship to adverse human reproduction outcomes.

Interim Report

The main purpose of the Interim Report was "to document progress and outline future work plans". In addition, interim conclusions and recommendations were offered in reference to trends in reproductive statistics, neural tube defects, other birth defects, the phenoxy herbicides (2,4-D and 2,4,5-T), aminocarb, and fenitrothion. The Interim Report also described the historical background concerning the use of chemicals in forestry, and the appointment by the New Brunswick Department of Health of several committees and Task Forces to study various aspects of this issue in reference to human health.

Supplementary Report

In the Interim Report, the Task Force reported that its toxicologists had not yet had an opportunity to review confidential studies conducted by the manufacturer of aminocarb and recommended that the Government of New Brunswick should not authorize its use until all of the recommendations of the 1980 Ecobichon panel had been satisfactorily completed. Shortly thereafter, the Task Force gained access to this information and considered that these recommendations had been met. This finding was presented in the Supplementary Report along with further comment on the desirability of additional toxicology studies, concern regarding contaminants, and concerns about federal policy regarding access to information on licensed pesticides.

Second Report

The Second Report should be viewed as a definitive document which meets the 1st, 2nd, 3rd and (partially) the 5th Terms of Reference. The focus was on trends and patterns of adverse reproductive outcomes, assessments of the toxicology and regulation of selected pesticides, and the development of an environmental chemical data base for New Brunswick.

Four recommendations pertaining to reproductive outcomes were made regarding:

- Maternal alpha fetoprotein screening for neural tube defects
- Vitamin supplementation and the possible prevention of neural tube defects
- Design of official health records
- Records linkage

Seven recommendations pertaining to toxicology assessments were made regarding:

- Canadian criteria for the performance of toxicology studies
- Access to essential regulatory information by government appointed inquiries
- Periodic regulatory review of licensed chemicals
- A product and environmental monitoring program
- An analytical chemist
- Use of primates in studies of teratogenicity and reproduction toxicology
- A maximum allowable contaminant level of 2,4,5-T

In addition, the Second Report provided comprehensive new information on the patterns and trends in a variety of reproductive outcomes in New Brunswick, provided detailed information on the reproduction toxicology of several important pesticides widely used in the province, detailed literature reviews of selected congenital anomalies, and described the development of a chemical data base, essential to the assessment of the 4th term of reference. A brief outline of proposals for further study was also presented.

Relationship of Previous Reports to Final Report

It is not intended in this final report to review all aspects of previous work. The focus in this report is on the 4th term of reference which involves assessment of association between chemical exposures and human reproductive problems. Much of the previous work, especially the Second Report, bears on this question in an indirect way. Wherever relevant to this assessment, reference will be made to this previous work, particularly in the section dealing with interpretation.

B. REVIEW OF WORK PRIOR TO FINAL REPORT - OVERALL STRATEGY AND
PREVIOUS FINDINGS

1. Reproductive health statistics were examined for the period 1921 to 1981 with emphasis placed on the most recent decade. Trends for New Brunswick were compared with those for the adjacent provinces of Nova Scotia, Quebec, and with Canada. Comparisons were made of all outcomes for which routine statistics were available: neonatal deaths, postneonatal deaths, infant deaths, stillbirths, perinatal deaths, birth weight and sex ratio.

In all three provinces, and in Canada as a whole, remarkable improvements in these outcomes were observed during this century. The rates of improvement in New Brunswick and Quebec were greater than seen in Nova Scotia and Canada as a whole, and all four jurisdictions now enjoy similar levels of reproductive outcomes.

Only stillbirths and perinatal mortality (which includes stillbirths) showed a consistent excess for New Brunswick. For this reason, the Task Force made stillbirths a focus of further study.

2. The selection of birth defects to be subjected to scrutiny by the Task Force was based on three general criteria: evidence of unusually high prevalence in New Brunswick, evidence that exposure to certain pesticides may be a plausible component of their etiology, and availability of sufficient data of adequate quality from the Canadian Congenital Anomalies Surveillance System.

Three anomaly categories were thus identified: neural tube defects which were documented to have generally high prevalence in the Atlantic provinces including New Brunswick, facial clefts for which animal studies had shown some experimental evidence of relationship to phenoxy herbicide exposure, and renal agenesis as renal abnormalities had also been seen in animal studies.

These categories were subjected to extensive literature reviews. In addition, original research was conducted by the Task Force into their patterns of occurrence in New Brunswick and ultimately into their possible association with chemicals. For this purpose, seven subcategories were constructed: anencephaly, spina bifida with and spina bifida without hydrocephalus, cleft palate, cleft lip with and cleft lip without cleft palate, and renal agenesis. Three groups of subcategories were also studied: total spina bifida, total cleft lip, and all major anomalies (combined).

3. The toxicology of major pesticides used in forestry spray programs was assessed with regard to reproductive effects. Specifically, this included the forest insecticides fenitrothion and aminocarb and the phenoxy herbicides 2,4-D and 2,4,5-T. Little published information was available on the insecticides, necessitating access to original study files maintained by Agriculture Canada and in some instances only by industry. In the case of one chemical, the herbicide Round-up[®], which has been recently introduced into the Canadian forest industry, the manufacturer (Monsanto) refused access to information despite several requests through available channels.

The findings of these reviews were presented in full detail in the Second Report. There was no evidence that either fenitrothion or aminocarb might lead to reproductive problems. In reference to 2,4-D, animal studies provide no evidence of teratogenic or reproductive risk. However, this compound is a weak mutagen and has the potential to cause chromosomal damage. In addition, 2,4-D is also subject to dioxin contamination, although not with 2,3,7,8-TCDD. Hence there remains some basis for concern. In the case of 2,3,7,8-TCDD and 2,4,5-T, the former is discussed with the latter as it is an inevitable contaminant. TCDD is mutagenic in some test systems, has a weak chromosome damaging effect, is teratogenic in mice at very low doses (kidney abnormalities and cleft palate), reduces fertility in rats, and has produced reproductive abnormalities in rhesus monkeys.

Thus it was that the Task Force indicated the need for caution in reference to the phenoxy herbicides (especially 2,4,5-T) although could find no basis for particular concern in reference to fenitrothion and aminocarb in the context of reproduction toxicology.

4. Due to concern about the potential for phenoxy herbicides to produce adverse human reproductive problems, a systematic literature review was undertaken of all relevant epidemiological studies. The majority of studies demonstrated no evidence of a relationship while a small number of studies suggested that such a relationship might exist, but this evidence lacked consistency, reproducibility and strength.

5. It had been apparent from the outset of Task Force activities that one could not address the 4th term of reference without having a data base from which to derive estimates of chemical exposure. Much of the first year of work was directed at developing such a resource, and the results of this effort were presented in the Second Report.

Briefly stated, an adequate data base on chemical use was constructed to address the issue of reproduction outcomes in relation to the major chemicals used in the forest industry over most of the past decade. Equivalent information was found not to exist for agriculture. Therefore, using land use patterns and a crop chemical use guide, an "agricultural chemical exposure opportunity index" was constructed. This enabled a series of studies to be undertaken addressing the 4th term of reference in the context of agriculture.

6. Patterns and trends of birth defects were identified within New Brunswick, and were compared where possible with up to 5 other provinces participating in the Canadian Congenital Anomalies Surveillance System (CASS), mainly during the 1970's. Selected birth defects, stillbirths and preterm births were assessed by county for rates of occurrence and seasonality. Birth defects were also assessed for long-term trends, county ranks, sex ratios, correlation between years and between anomalies.

This has been by far the most comprehensive assessment of the patterns and trends in birth defects ever undertaken for a Canadian province.

Despite the lower rates of total anomaly reporting, New Brunswick demonstrated consistently higher rates of neural tube defects than other provinces participating in CCASS.

When counties were ranked by frequency of anomaly for nine specific anomaly categories and the combined category "total anomalies", counties within the Saint John River Basin* appeared to have generally higher ranks than other counties, and were more often associated with aberrant seasonal peaks. Some indication of an approximately annual cyclic pattern in stillbirths and preterm births associated with the watershed was also obtained. Some other counties outside the watershed area (e.g., Northumberland) also exhibited a relatively higher frequency of anomalies.

*It is not suggested that the terms "river basin" or watershed are anything other than a way of describing areas that may have a number of factors in common with one another.

C. RESEARCH STRATEGY FOR FINAL REPORT

The investigation of associations between the use of chemicals in the environment and patterns of adverse human reproductive outcomes has been a complex, difficult and time-consuming task. The occurrence of problems such as stillbirths and birth defects is believed generally to have multifactorial origins. The difficulty in documenting chemical use patterns constitutes a major obstacle to the study of relationship. Methods of study also have inherent strengths and limitations. Such difficulties, which are common to all studies into complex environmental health issues, are discussed in some detail elsewhere in this report (Section G). At this stage, the following outline describes the overall strategy of new studies included in this final report.

There have been, in addition to studies presented in earlier reports, three distinct types of further study:

Geographic Correlation Analyses

Analyses for Temporal Association

Case Control Studies

Geographic correlation analyses address the question of whether there is any evidence of association within counties, between the amount of exposure and the frequency of birth defect occurrence, by major subcategories across all quarters during the study period.

Analyses for temporal association have been undertaken in two ways. Firstly, the correlation analyses have been carried out at four quarterly lag intervals. This means that the exposure is correlated with the frequency of an outcome, not only within the same quarter, but also with outcome frequency 1, 2

and 3 quarters later respectively. This approach takes into account the time required for fetal development, as well as possible delays between chemical application and actual exposures.

The second approach to analyses for temporal association involved comparison of mean rates of occurrence in each county for each of the 10 outcomes of interest (7 birth defect categories, all anomalies combined, stillbirths and premature births) when spraying took place, with the corresponding mean rate in the subsequent three quarters (and at all quarterly lag intervals from 0 to 3).

Several case control studies were carried out. A case control study starts with identification of persons with disease (e.g., a birth defect subcategory) and a suitable reference group of persons without disease. The relationship of exposure to disease, if any exists, is judged by comparing the case and control groups with regard to the exposure measure. The strength of such association is assessed by the magnitude and statistical significance of a standardized risk ratio.

These distinct analytical approaches are viewed as complementary, but it is of fundamental importance to recognize that they are not of equal merit in assessing possible relationships. Specifically, the geographic correlation and temporal analyses are of a much lower order of rigour than case control studies in addressing the fourth term of reference. Such studies are based on aggregated data for areas or times which are then assessed in terms of associated levels of outcomes, aggregated for the appropriate time and place. They are inherently incapable of assuring us that an elevated frequency of outcome, associated with an elevated degree of exposure, will, in fact, be

found to be true of individuals with that outcome. Such an association may be direct, but might also be quite indirect and have no bearing on presence or absence of association at an individual level. The case control study design, by contrast, utilizes information on the estimated exposure for individuals and is much more able to speak to a direct association.

Thus, at the outset, it is important to indicate clearly that the results from these conceptually distinct studies are not of an equal order of merit and that greatest importance should be attached to the findings of the case control studies. With this perspective, the results from all studies, including those presented in earlier reports, are taken into account in the final interpretation and conclusions.

D. THE CHEMICAL DATA BASE - ESTIMATION OF CHEMICAL EXPOSURES

In the Second Report of the Task Force on Chemicals in the Environment and Human Reproduction Problems in New Brunswick, a section was devoted to the development of an inventory of chemicals used in New Brunswick during the period 1970-1981. The following is a continuation of the discussion on the agricultural use of chemicals as well as a discussion of the use of home and garden pesticides and their contribution to the total of all pesticides used in New Brunswick.

Agricultural Pesticide Data Base

Several different approaches to establishing an agricultural pesticide data base were attempted.

When the Task Force initially collected data on chemical use in agriculture, information was not available on actual agricultural pesticide usage patterns in either New Brunswick or representative jurisdictions elsewhere. The Task Force thus decided to record fluctuations in crop production per year as a surrogate for pesticide usage. The underlying assumption for this approach is that for a given crop, pesticide usage is a function of crop size. An attempt was made to estimate pesticide usage by using information gleaned from the New Brunswick Pesticide Permits and information extracted from the Guide to Chemical Weed Control. This information was presented in the Second Report on page 218.

Pesticide Usage Patterns for both Nova Scotia and Prince Edward Island became available to the Task Force during 1984. The information is in the form of quantity of active ingredient typically used in agriculture per hectare of crop in these two provinces, and is crop specific. These usage patterns are

tabulated in Table D1 along with the information extracted from New Brunswick pesticide permit records and the Guide to Chemical Weed Control.

For the purposes of illustration, a predictor of pesticide usage was derived by examining the estimates obtained for Nova Scotia, Prince Edward Island and New Brunswick and the Guide to Chemical Weed Control and taking an estimate of central tendency. (see footnote, table D1-for detail on method) This predictor was then used to project the total agricultural pesticides used in New Brunswick, by county. The data are graphed in Figure 1. For comparative purposes, a similar figure was constructed for forestry pesticides using data from the Task Force's Second Report. These data are graphed in Figure 2.

A wide variation among these different approaches to estimating agriculture usage patterns (table D1) is immediately obvious. Two explanations emerge: (1) pesticide usage from area to area varies greatly, and/or (2) the use of agricultural pesticides today is poorly understood and considerable study is needed before one will really know what and how much is being used. Both explanations are probably correct. The variation observed among the various sources of data reinforces the Task Force's earlier position that crop production figures are more accurate than any alternate estimate that could be developed for actual pesticide usage.

Another problem encountered in the initial data collection was the absence of data for non-census years. The data base developed for agricultural practices contained data for the census years 1971, 1976 and 1981. During the intervening years, only limited census data were collected by the regulatory

FIGURE 1

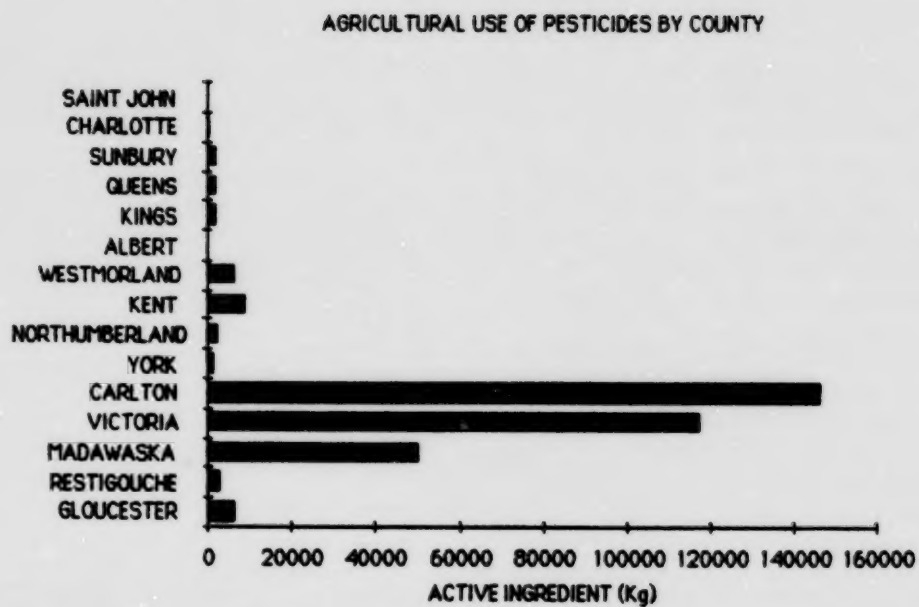
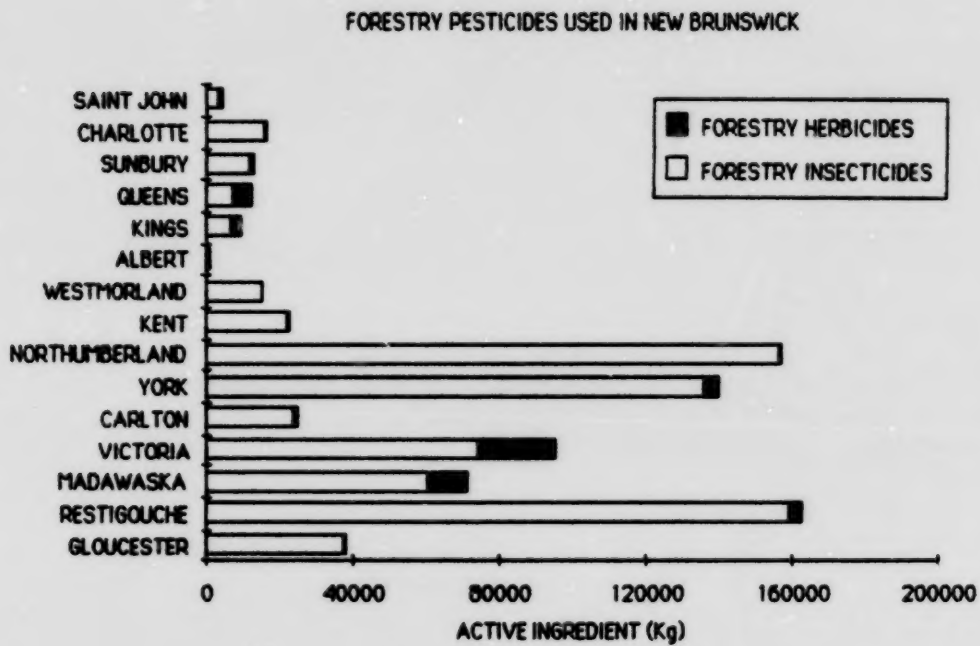


FIGURE 2



bodies. A figure produced for the Second Report which illustrated the wide variation in provincial crop production, on a yearly basis, indicated that simple extrapolation between two census years is impossible. However, the Task Force required data for the intervening years as well as the census years so that the fourth term of reference could be addressed. Therefore possible additional sources of information for intervening years were sought.

Staff members from the New Brunswick Department of Agriculture and Statistics Canada were interviewed. The Task Force learned that Statistics Canada carries out annually a limited random survey of small and large farms to derive an estimate of provincial totals for crop production. These data cannot be extrapolated to the county level. Information based on remote sensing was also sought by contacting researchers who had recently surveyed potato acreage in the Saint John Valley using Landsat satellite data, but these data also were not appropriate for analysis at the county level. Therefore, our conclusion was that agricultural statistics at the county level are not available for the intervening years. This lack of data is unfortunate because it prevented the Task Force from examining, by way of correlation and temporal analyses, possible association between agriculture pesticide exposures and reproductive outcomes.

A further requirement of the Agricultural Chemical Data Base was the exact location within the county where pesticides are applied. The following approaches were used to obtain this information:

1. The New Brunswick Department of Environment has been collecting vendors' sales records on commercial pesticides sold within the province since 1980. Data on the type of pesticide, quantity sold, and purchaser are collected by officials of the Department of Environment. A summary of these data is

published yearly in terms of amounts sold in each Health District as well as the amount sold in the province as a whole. This inventory is published annually and is called Pesticide Usage in New Brunswick. Unfortunately, this information was not collected during the 1970's, the major period under investigation by the Task Force. It is well known that pesticide usage patterns have changed substantially during the 1970's, making extrapolation of data from the 1980's to the 1970's inadvisable. Nevertheless, these current data do represent valuable information and should become useful for future studies. In order that this information can be linked to health records such as those kept in the Canadian Congenital Anomalies Surveillance System, data should be available at local (e.g., county and subcounty) levels of aggregation.

2. The next step in acquiring information on the location of pesticide use involved obtaining agricultural maps outlining the exact location of crops and farms in New Brunswick. The Canada Land Survey began to develop such maps in the late 1960's but, for reasons unknown to the Task Force, completed only half the task. These maps would have provided an ideal alternative.

3. The final approach was to use the Soil Capability for Agriculture maps, also produced by the Canada Land Survey. Although these maps do not give the exact location of crops and farms, they do indicate which lands are most suitable for agriculture. These maps recognize seven classes of land use. The first three classes are considered capable of sustained production of common cultivated crops, the fourth is marginal for sustained arable culture, the fifth is capable of use only for permanent pasture or hay, the sixth is capable of use only for wild pasture while the seventh is considered incapable of use for arable culture or permanent pasture. Urban lands were included within this last category.

Actual agricultural practices tend to follow this classification scheme. Therefore, the areas on the map depicting soil classification 1-3 were used as a proxy for active crop production. As crop production is related to pesticide usage, areas depicting soil type 1-3 can also be used as an index of potential pesticide usage and therefore potential pesticide exposure, taking into account the times of year during which pesticide application is recommended. The resulting index is therefore more than a simple reflection of soil capability, as it incorporates a general schedule for chemical applications.

Home and Garden Pesticides

The Task Force sought data which would give an estimate of the amount of pesticide used around the home and an indication of how this would compare to the total quantity of pesticide used in New Brunswick.

The only data which the Task Force was able to obtain was from a Pesticide Industry Survey conducted in 1981 by Touche Ross Chartered Accountants which indicated that the per capita expenditure in Canada for Home and Garden Pesticides is \$2.00. Local stores were surveyed to determine how much pesticide could be purchased (mass of active ingredient) with this amount of money. This information along with New Brunswick population census data, was used to extrapolate to the New Brunswick situation. Figure 3 illustrates the proportion of Home and Garden Pesticides compared with those used in Agriculture and Forestry. The Home and Garden Pesticide data was also graphed by county, for illustration purposes (Figure 4).

Although the percentage appears small, it is probably this category that poses the greatest potential human exposure. The storage and use of these chemicals in and near living spaces, combined with the usual lack of protective measures in the home, present special problems (e.g. accidental poisoning of

FIGURE 3

CATEGORIES OF PESTICIDES USED IN NEW BRUNSWICK

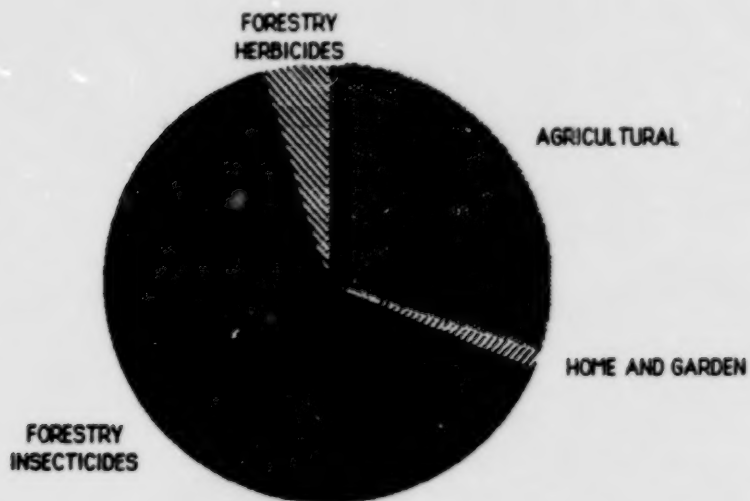
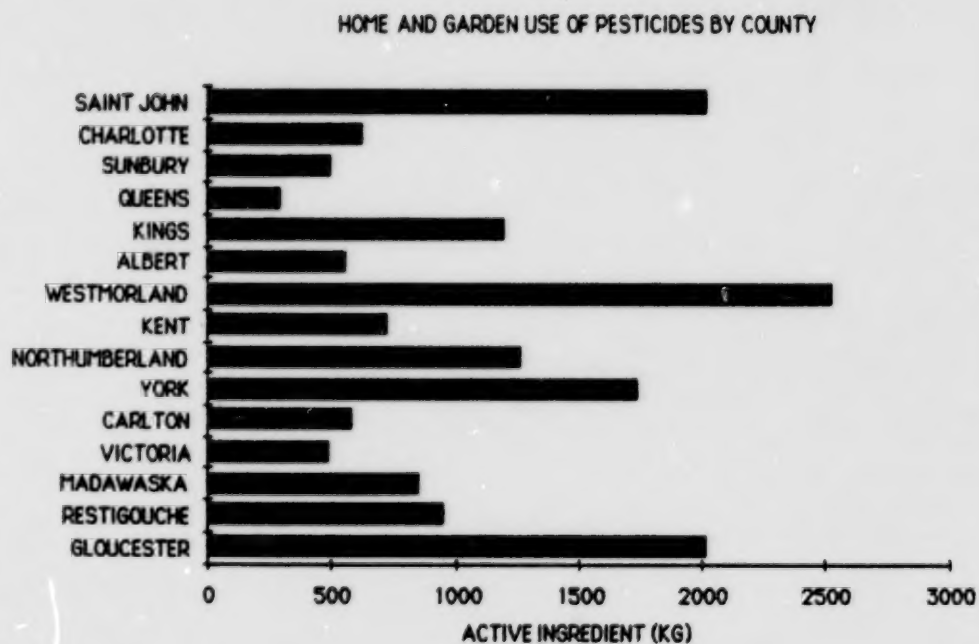


FIGURE 4



children). Thus compilation of statistics on home and garden pesticide use would seem to be essential area for future development. The absence of such data imposed an important limitation on the work of the Task Force.

Determination of Exposure Index

An index of individual exposure was required in the case-control studies for each case and control who may have been exposed to forest or agricultural chemicals at any time during an embryologically relevant exposure risk window (Case-Control Studies, Section F). An exposure potential was determined for each of the following categories: fenitrothion, aminocarb, phenoxy herbicides and the agriculture chemical exposure opportunity index (ACEO Index). The forestry maps discussed in the Second Report (pages 213-215) were used to calculate fenitrothion, aminocarb and phenoxy herbicide potential exposures. The Canada Land Inventory Soil Capability for Agriculture maps were used to calculate the ACEO Index, for the potential exposure period of June to October each year. Exposure was calculated as follows:

1. For each case or control that fell within the risk window (i.e., the critical period or organogenesis or foetal development during which a teratogenic effect would be considered embryologically plausible), the mother's residence (town, city, etc.) as stated on the infant's birth certificate, was determined and located on the appropriate map.
2. A transparent circle (a template) with a radius equivalent to 5 kilometres was placed on the map and the centre of this circle was aligned with the address as defined in 1 above. The circle, which represents an area of approximately 78.5 square kilometers, contained 100 dots and each dot was so positioned so that it represented 1% of the area of the circle.
3. Keeping within the boundary of the circle, the number of dots were counted which superimposed the area of interest on the map, (e.g. for fenitrothion

potential exposure, the number of dots on the template were counted which lay on top of the area of the map depicting area sprayed with fenitrothion. If none of the area of the template superimposed the area of the map depicting fenitrothion spraying, then the potential exposure was represented by 0% (no dots) whereas if half of the 5 kilometre radius circle superimposed a spray area, then the potential exposure to fenitrothion was 50% (50 dots in the circle). Determination of potential exposure for aminocarb and the ACEO Index was accomplished in a similar manner. Because of the imprecise areas on the map depicting phenoxy herbicide spray areas, only a plus (+) or minus (-) score was assigned for this group of chemicals, denoting presence or absence of potential exposure within the defined areas.

Consolidation

In the Second Report of the Task Force, a figure was produced which showed the various types of commercial pesticides that are in current use in New Brunswick. This figure revealed that greater masses* of pesticides used in the province are aerially applied (99.5%) than are applied by ground application procedures (0.5%). Of those chemicals applied aerially, insecticides used for forest protection represent the largest mass (88%), agricultural fungicides represent the next largest mass (8%), while forestry and agricultural herbicides account for the remainder. In contrast to this, herbicides represent the largest mass (81%) of those pesticides applied by ground techniques with insecticides and fungicides representing 12% and 7% respectively.

* Mass refers to active ingredient and does not include solvents and emulsifiers.

The Task Force estimates that 1,100,000 kilograms (active ingredient) of pesticides are used in New Brunswick annually for forestry and agricultural practices. The New Brunswick Pesticide Usage Inventory accounts for approximately 80% of these chemicals.

In reference to the Forestry Chemical Data Base, the Task Force feels confident that satisfactory insecticide use data exist and were freely made available to the group during its deliberations. The group feels that the record keeping practices of the New Brunswick Department of the Environment and those of Forest Protection Limited in reference to forest insecticide programs should serve as a model for other jurisdictions carrying out similar activities. Forestry herbicide data are available only as far back as the mid 1970's and the quality of these data prior to about 1980 is questionable. The herbicide data collected during the 1980's appears to be of good quality.

In reference to agricultural chemical information, considerable problems in obtaining relevant data for the period under study were encountered.

Records of chemicals used in agricultural practices do not exist for most of the 1970's. The Department of the Environment has been collecting vendors' records since 1980 and it would appear that these data should be valuable for future studies, but the Task Force was not able to use these for the present study. The Task Force was pleased with the system New Brunswick Environment has recently developed to collect these data, and the apparent level of reporting (80%) achieved. Efforts should be expanded to encourage an even greater level of reporting. An audit system should be put in place to ensure the completeness and precision of the collected data.

Due to the lack of pesticide usage data for the agricultural industry during the 1970's, the Task Force relied on Soil Capability maps to serve as a basis for an Agricultural Chemical Exposure Opportunity Index (ACEO Index). The lack of crop production statistics for non-census years made it impossible for the Task Force to examine, by way of correlation analysis and comparison of mean rates, the county level association between the ACEO Index and reproductive outcomes. Actual chemical use patterns, had they been available, could have greatly improved the precision of the analysis. Case control studies were however, feasible with this index, permitting assessment of association at an individual level.

An attempt was made to develop a home and garden chemical data base, primarily to bring this important chemical category into perspective. The data were inadequate for use in any type of analysis for association. The Task Force does recognize the importance of these chemicals and believes that this could represent the most significant direct exposure potential of all categories considered.

E. CORRELATION AND TEMPORAL ASSOCIATION BETWEEN NON-AGRICULTURAL
PESTICIDE EXPOSURES AND REPRODUCTIVE OUTCOMES

Events are said to be associated when they occur more frequently together than one would expect by chance. Association does not necessarily imply a causal relationship. Correlation is a measure of association that indicates the degree to which two or more sets of observations fit a particular relationship (usually linear). Statistical analyses investigating the association between measures of exposure to selected chemicals (Appendix I) and outcomes of interest (Appendix II) took three forms: correlation coefficients, comparison of mean rates across specified time intervals, and case control studies. Correlation analyses and comparison of mean rates are described in this section of the report, and deal with evidence for association at the county level. Association at the individual (person) level is assessed by case control studies, presented in the subsequent section.

The analyses presented in this section focus primarily on pesticides used in forestry although data on usage for clearing power line right-of-ways are also included. Seven pesticide categories are considered: (1) fenitrothion formulations, (2) aminocarb formulations, (3) other forest insecticides, (4) herbicides with some phenoxy component, (5) phenoxy herbicides only, (6) chlorinated herbicides and (7) non-chlorinated herbicides. Categories 1, 2 and 3 were analysed according to mass (kilograms of active ingredient per county) while categories 4-7 were based on area (number of acres sprayed per county), as described in Section D (page 20).

Ten reproductive outcome categories were included in the analyses: anencephaly, spina bifida with hydrocephalus, total spina bifida, spina bifida without hydrocephalus, cleft palate, cleft lip, total cleft lip, cleft palate

with cleft lip, renal agenesis, a combination of 40 anomalies ("all anomalies"), stillbirth and preterm birth* (Appendix II).

METHODS

The general strategy embodied within this section of the report is to carry out a search for associations using geographic correlation analyses and comparisons of mean rates. The actual methods will be described shortly, but it is important to emphasize at this stage that these do not presume to test hypotheses. Nonetheless evidence from this search for association will be considered later in the report when the issue of causality is addressed. Briefly, geographic correlation analyses address the issue of whether there is evidence of an exposure-response association within counties, while lagged correlations and comparison of mean rates of outcome between sprayed and non-sprayed periods address the issue of temporal association (i.e., does the presumed cause precede the effect and to what extent?). In addition to these approaches the issues of embryological plausibility and robustness are also considered.

1. Geographic Correlation Analyses

The strength of the association between the frequency of occurrence of the 10 health outcomes and the degree of exposure to each of the seven chemical groups as identified earlier in this section of the report (and at all quarterly lag intervals 0 to 3) in each county was measured with the Pearson

* Preterm birth, for the purposes of this report refers to births in the range of 20-27 weeks gestation. This may also be considered as "extreme immaturity".

product-moment correlation coefficient. The analyses involved time periods (i.e. quarters) when spraying actually took place.*

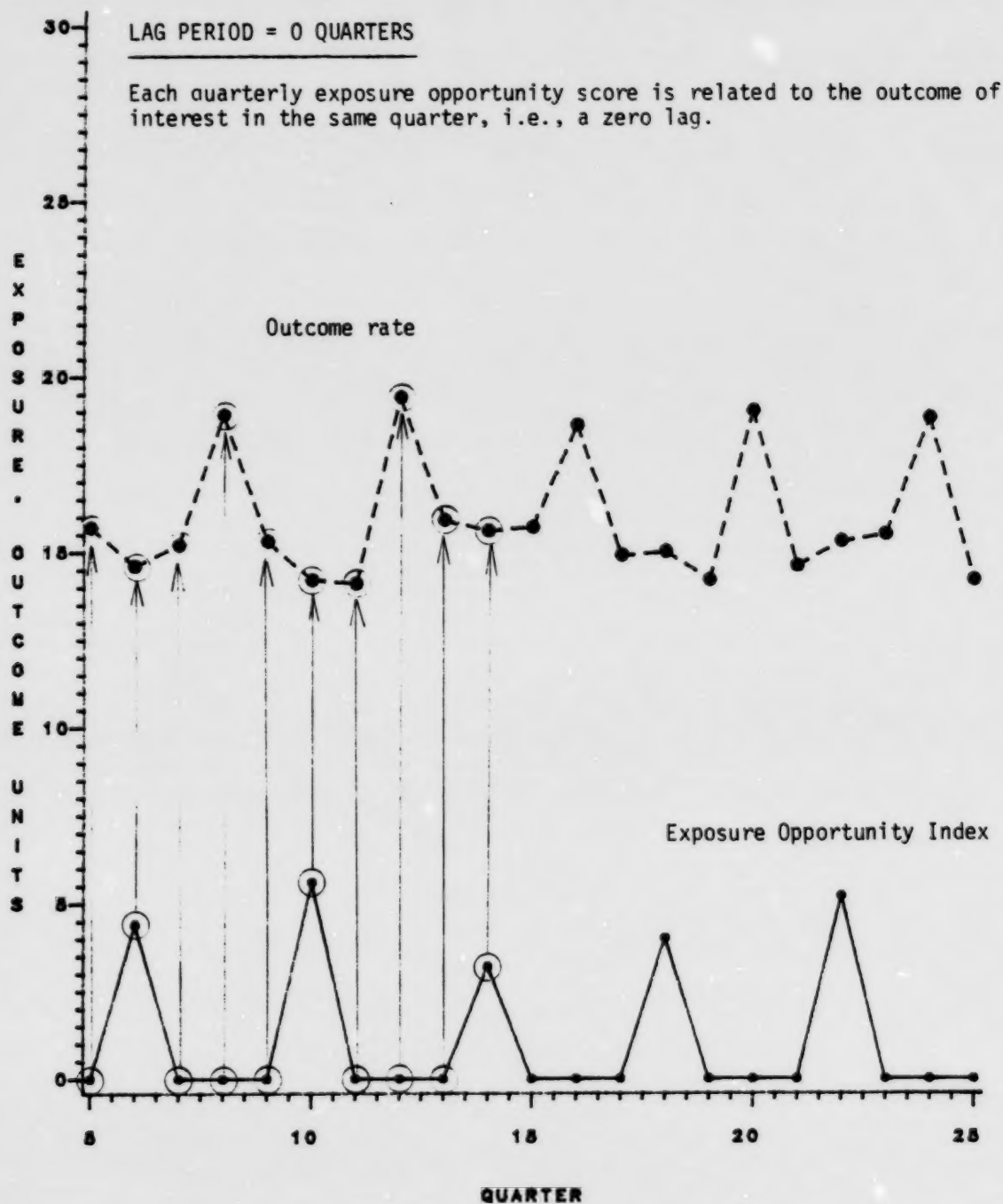
There are advantages and disadvantages to this approach. The principle disadvantage is the loss of power that derives from deletion of data points when no spraying actually occurred, effectively reducing the sample size. In addition, while this approach attempts to locate evidence of a dose response association among county periods during which different levels of actual exposure took place, the possibility of a dichotomous (spray-no spray) difference in outcome is ignored. The theoretical advantage of this approach is based on the observation that non-spray values are not randomly distributed in time, because spraying tends to occur at particular times of the year. Thus, a seasonal difference in rate of adverse reproductive outcomes might confound an analysis which included the larger number of non-spray values derived mainly from other seasons of the year. The judgement to proceed with a more limited geographic correlation analysis was made in the context that it would be complemented by the comparison of mean rates between sprayed and non-sprayed periods.

* Individual chemical sprays are rarely used in any more than a single calendar quarter, thus 75% of all spray-outcome pairs will have a spray value equal to zero. (For example, the analysis of a single spray-outcome combination in all 15 counties from 1973-1977 inclusive (= 28 quarters) produces $15 \times 28 = 420$ data points, at least 315 of which are zero for a particular spray value. In fact, more than 315 will be zero because some counties are not sprayed with that particular chemical in a given year.)

Correlation was chosen as a simple, well-known statistical method for screening the large number of combinations between chemical group, outcome and lag in this data set (i.e., 7 chemical groups x 4 lags x 10 outcomes across 15 counties). Because exposure may have the potential to produce effects over a wide range of time, depending on gestational age and type of outcome, correlation coefficients were calculated between outcome and spray in all counties over the available time period for each of 4 quarterly lag intervals. The results of the 280 correlation analyses are shown in Tables E1-E4.

For the purpose of lagged analyses, the year is viewed as consisting of 4 quarters. Within each quarter, outcome may be correlated with exposure; this is considered a lag 0 analysis. However, if an exposure-outcome relationship exists, it is possible that the outcome might be delayed 1, 2 or even 3 quarters, taking into account the time required for fetal development from organogenesis to birth. In addition, some (unknown) delay might exist between the time of spraying and certain types of indirect exposure (e.g., water, food). For these reasons a series of four analyses have been carried out for all quarters in the study, corresponding with lags 0, 1, 2 and 3. This is illustrated in figure 5.

SCHEMATIC ILLUSTRATION OF LAGGED COMPARISON



DATA ARE FICTITIOUS

Correlation coefficients fall within the range -1 to +1. The null hypothesis, that there is no relationship between spray and outcome, would be supported by correlations approaching zero. Intermediate correlations could result from random variation, or might reflect the existence of some degree of association. If amount of spray and rate of outcome are related, the expectation would be a high positive correlation coefficient. Negative correlations could similarly result either from random variation or from inverse association. The larger the coefficient (e.g., approaching + or -1) the stronger the evidence of positive or negative association between the spray factor and the reproductive outcome under study.

Since the product-moment correlation summarizes only the degree of linear association, non-linear relationships might exist (e.g., quadratic or threshold types) but may be missed with this technique. However, without prior information on the form of spray-outcome associations (if any exist), the linear model is a justifiable one to assume. In order to detect possible non-linear exposure-outcome patterns, many of the combinations were also graphed and examined visually.

Because different chemical groups were used over different periods of time and in different parts of the province, the coefficients in each column are based on a different number of data points (which are shown in the tables). Since the critical value for statistical significance is related to the sample size, the significance of various correlation coefficients based on different numbers of data points cannot be compared strictly at face value. However, the significance of each correlation has been determined and all of those falling outside the nominal level of $\alpha = 0.05$ have been flagged. Significance testing is not used here as an end in itself but only to indicate which coefficients may be worthy of further attention.

It is also recognized that, in randomly distributed data, where many correlation coefficients are calculated, there should be a roughly equal distribution of positive and negative coefficients, and that most coefficients should be relatively small in magnitude. Similarly at the arbitrary level chosen for statistical significance ($\alpha = .05$), approximately 1 in 20 such tests will be significant by chance alone. Caution should be exercised in attaching any importance to such findings.

Correlation might reflect a causal association but might also be non-causal or even "nonsense" due to random patterns of occurrence, multiple calculations or testing. Two additional steps are taken in this analysis to eliminate obviously non-causal or random association: assessment of embryological plausibility and assessment of robustness. These steps do not exclude the possibility that remaining associations might still be non-causal or "nonsense", but reduce to a more manageable level the number of associations which need further consideration.

Embryological plausibility is accorded only to those elevated correlation coefficients which are observed to occur at intervals consistent with recognized periods of fetal organogenesis. Conversely if a positive correlation were to occur at a lag interval that is embryologically implausible, then it should be rejected. The gestation period for most birth defects (an average of 39 weeks) is only slightly less than for normal births. The defects themselves, however, originate from critical periods during the first trimester of pregnancy. Thus, it may be determined that a correlation between a maternal exposure and a full-term fetal outcome with a birth defect in the same quarter (lag 0) in a given year must be quite implausible.

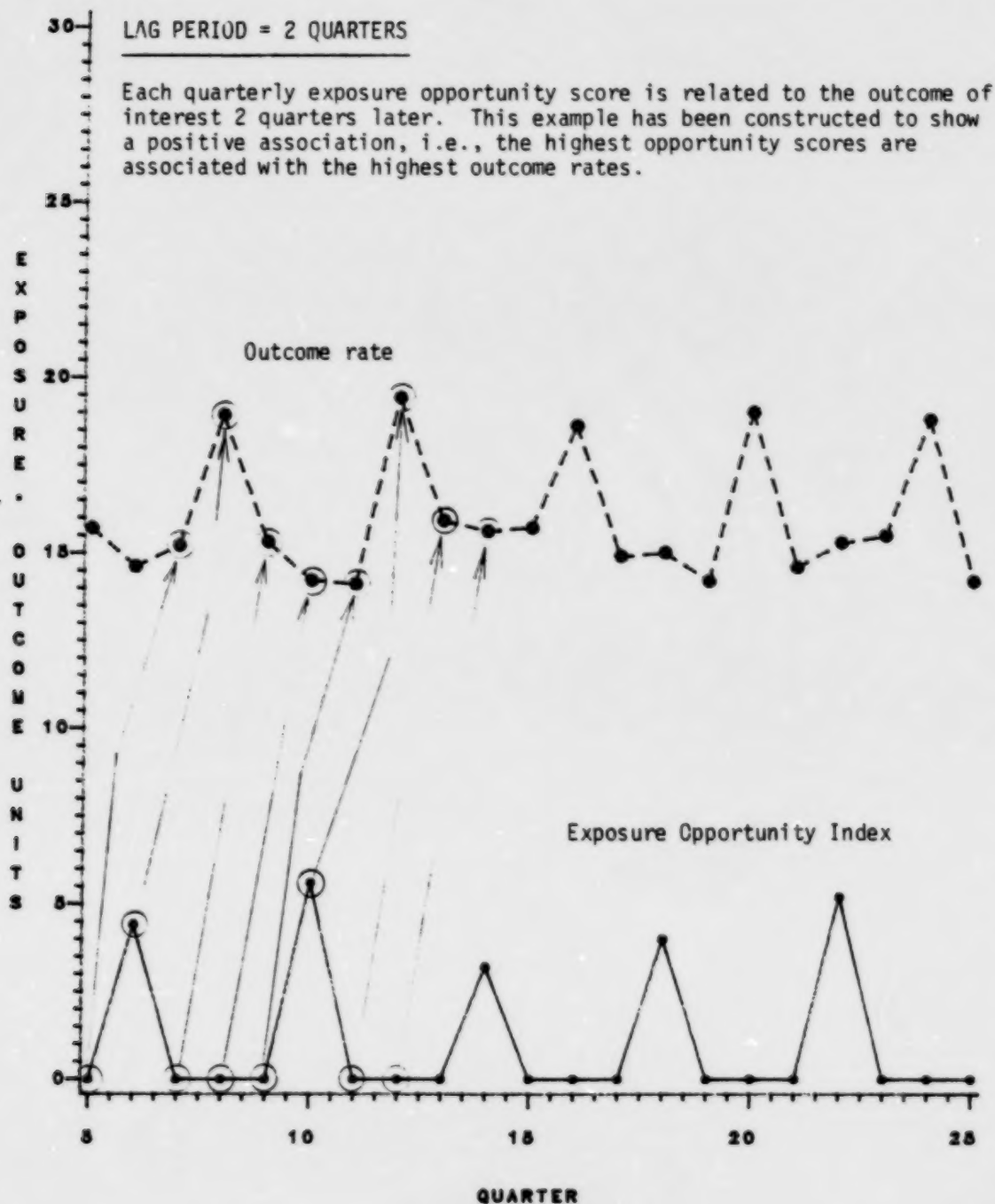
Similarly there is no likelihood of such a biological relationship occurring at lag 1, and only a small likelihood at the end of lag 2. Greatest likelihood exists at lag 3.

This means that elevated correlation coefficients relating a birth defect outcome to exposure at lags 0 and 1 can be excluded from further consideration, regardless of their strength or statistical significance, because they make no embryological sense. Some consideration may be given to a lag 2 correlation, given the occurrence of birth late in that lag related to conception early in lag 0, although clearly the most embryologically plausible correlation should be at lag 3. A schematic illustration of a lag 2 comparison is presented in figure 6.

FIGURE 6

-32A-

SCHEMATIC ILLUSTRATION OF LAGGED COMPARISON



DATA ARE FICTITIOUS

In the case of stillbirths (defined as 28 weeks of gestation or greater) an acute effect may be judged to be plausible. Thus correlation at lags 0 and 1 (equivalent to 3rd and 2nd trimester effects) may be considered generally more plausible than at lags 2 or 3. However, a long-range effect of stillbirth relating to exposure in the first trimester (requiring a lag 2 or lag 3 analysis) could still occur if associated with an anomaly that is incompatible with or detrimental to life.

It was often suspected that the overall correlation may be heavily influenced by extreme value data points on the spray measure. To assess this issue of "robustness", several high correlation spray-outcome combinations have been examined by recalculating the correlation after dropping 1, 2, 3 and up to 4 of the data pairs involving the highest spray values (Table E5). In the event of a "true" association, the value of the correlation coefficient should not fluctuate wildly when a few points are dropped.*

* To illustrate this approach (Table E5), originally "strong" associations whose effect seems due to a few outliers are marked with an asterisk. In addition, a few originally "weak" overall associations have been investigated because it appeared, from the scatter diagrams, that an outlier was depressing the value of the underlying association. These are marked by an asterisk in parenthesis.

2. Comparison of Mean Rates

A comparison of the mean rate of occurrence in the 10 outcomes of interest when spraying took place with the corresponding mean rate in the subsequent three quarters (and at all quarterly lag intervals from zero to three) was made for each county-chemical combination (Table E6).

The purpose of this analysis is to further assess whether a temporal association may exist between chemical exposure and occurrence of adverse reproduction outcomes. The practical question here is to establish whether presumed "exposure" is followed by an elevation in rates of "outcome", and if so by what period of time. This analysis complements the lagged correlation analysis in that it includes data for counties and quarters during which no spraying took place.

The nature of this analysis is to assess the direction of the difference in average rate between sprayed and non-sprayed quarters for individual counties. No account is taken of the magnitude of the differences. These directional analyses are intended only to "flag" possible associations and serve to complement the temporal inferences from the correlation analyses. In instances where the results of correlation analyses and comparisons of mean rates are in conflict, less importance should be accorded to these findings. Where the two approaches provide mutually supportive evidence of temporal association, this should be viewed as more coherent information.

Significance testing was carried out using the sign test on the distribution of positive and negative directional differences across all counties, for a total of 10 categories of adverse outcome, 7 chemical exposure categories, and 4 lag periods. Thus a total of 280 such tests were performed,

enabling some further assessment of the degree of statistical significance that may be accorded to these directional observations, although it is recognized that with this number of tests performed, 14 significant values should be expected at a probability level of $\alpha = .05$.

RESULTS

1.) Correlation Analyses

Correlation analyses (Tables E 1-4) show a total of 19 nominally ($p \leq 0.05$) significant coefficients. Approximately 14 would have been expected by chance at this level of probability (1 in 20). Forty five per cent (104/231) of the non-zero coefficients are negative (approximately the number that would have been expected in randomly distributed data) suggesting a very general overall impression of no (linear) association between levels of potential exposure to chemical sprays and reproductive outcomes. All health outcomes under study show at least one significant correlation except premature (20-27 weeks gestation) livebirths. The 19 significant coefficients are dispersed among the remaining 9 outcomes: "all anomalies" (category 8) has the highest number with 5, the insecticides account for 6 significant coefficients (6 expected) and the herbicides account for 13 (8 expected). Eleven of the latter are associated with phenoxy herbicides (6) or herbicides with any phenoxy component (5). Most (16) of the significant correlations occur at lags 0 (8) and 2 (8). All of the significant coefficients are positive whereas one would have expected an approximately equal distribution of significant positive and negative coefficients in the absence of association.

Great caution is required in assessing these correlation coefficients.

Acceptable interpretations require a plausible embryological rationale. For example, only in the case of stillbirths and premature births could one reasonably expect a cause and effect relationship to an exposure in the same quarter as the outcome, although such effects could occur also at other lag intervals particularly at lag 1 assuming an acute or short-term effect.* Birth defects, ascertained predominantly in live births, require exposure at a critical period of embryonic development (in the first trimester) and sufficient gestational age to sustain a live birth. Such effects are generally most likely to occur with a lag of three quarters, but could also occur with a lag of 2 quarters depending (in part) on the time of conception during the first quarter. These biological realities must be taken into account, in order to differentiate those correlations which may have some biological basis from those which may simply be "nonsense correlations" due to chance or co-incidental non-causal association.

Taking into account the foregoing comments, the following resolution of results from these correlation analyses are now tabulated:

* Some birth defects (almost exclusively syndromes) are the result of exposures to specific drugs or chemicals. Whether most defects (and syndromes) require an "exposure" is far from established. Other factors such as genetic predisposition, maternal biological characteristics, or deficiencies may be more important. If pesticides are of any importance, it must be because of maternal exposure at biologically plausible periods.

EMBRYOLOGICALLY PLAUSIBLE SIGNIFICANT CORRELATIONS

<u>Chemical</u>	<u>Significantly Correlated Outcome</u>	<u>Lag (Quarters)</u>	<u>Robust?</u>
Fenitrothion	Anencephaly	2	YES
	Spina Bifida without Hydrocephalus	2	YES
	"All Anomalies"	3	YES
Aminocarb	Cleft Lip	2	NO
Other Insecticides	Renal Agenesis	2	YES
Herbicides with Any Phenoxy	Stillbirths	0	NO
	Cleft Palate	2	NO
	"All Anomalies"	2	YES
	Cleft Lip	3	YES
Phenoxy Herbicides	Stillbirths	0	NO
Chlorinated Herbicides	NIL	N/A	N/A
Non-chlorinated Herbicides	NIL	N/A	N/A

Thus only 10 of 19 statistically significant positive correlation coefficients are considered embryologically plausible. It was noted earlier that chance alone would generate approximately 14 statistically significant findings. Chance could therefore account for some or all of these 10 findings. Whether this is so in any individual instance can be partly assessed by reference to robustness (see Methods - page 6 , and Table E5). Robustness calculations for insecticide associations reveal that associations between fenitrothion and anencephaly (lag 2), spina bifida without hydrocephalus (lag 2), and "all anomalies" (lag 3), are all fairly robust, while for aminocarb the association with cleft lip (lag 2), loses its robustness after deleting four

data points. The association between other insecticides and renal agenesis (lag 2) is judged to be robust. Of the 4 embryologically plausible statistical associations with herbicides with any phenoxy component, the associations with cleft palate and stillbirths are clearly lacking in robustness, while the correlation for "all anomalies" remains relatively stable and that for cleft lip actually increases. Similar attention to phenoxy herbicides indicates that the association with stillbirths is not robust.

Embryologically plausible robust statistical associations, based on these correlation analyses are noted in the table on page 37 and summarized on page 44 (Principal Findings).

2.) Comparison of Mean Rates

Initial comparison of mean rates was assessed in an arbitrary non-parametric manner, note simply being taken of any set of observations that appeared to deviate from an approximately 50/50 distribution among counties between positive and negative directions.* Such comparisons were necessarily quite limited in situations where not all counties were exposed to more selectively used chemicals (e.g. herbicide subcategories). The findings of these analyses are now described in reference to each pesticide category, subject to assessment of embryological plausibility.

*In consolidating this information, significant testing was also carried out using the sign test on the distribution of positive and negative directional differences, as outlined in Section E - Methods.

I. Insecticides

Fenitrothion: The most notable observation* is the higher frequency of stillbirths at 1 quarter lag, where rates were elevated in 12 of 15 counties (Table E6).

Aminocarb: The only notable observation was the greater frequency of stillbirths, one quarter following the time of spray (10/15 counties) (Table E6).

Other Forest Insecticides: Again, the only notable observation was a higher rate of stillbirths with a lag of one quarter following insecticide application (12/15 counties) (Table E6).

In view of the apparent temporal association between each of the three insecticide categories and the occurrence of stillbirths, at a lag of one quarter following application, this finding was examined in reference to the correlation analyses for equivalent lag intervals. The relevant correlation coefficients were all close to zero (.028, .009, -.133) and cannot be viewed as supportive of association. Nonetheless, in view of this suggestion of a temporal association at an embryologically plausible interval (equivalent to a second trimester exposure), and public concern about forest insecticides in particular, case control studies were carried out in reference to both first and second trimester exposure windows (presented later in the report).

* Anencephaly and spina bifida with hydrocephaly showed a mild tendency to occur at higher rates at a lag of 2 quarters following fenitrothion exposure (in 9 of 15 counties). Spina bifida without hydrocephaly showed a similar trend at a lag of 3 quarters (in 10 of 15 counties). By contrast, the "all anomalies" category more often demonstrated higher rates at lag zero (in 11/15 counties). These observations are noted "for the record" but are considered very weak and easily explicable on the basis of chance variation. In the case of "all anomalies", an underlying embryological relationship can be ruled out at lag zero.

II. Herbicides

Herbicides with Any Phenoxy Component: When mean rates of outcome were compared across lag intervals, no remarkable findings were observed in reference to any reproductive abnormality.

Closer examination was made of those outcomes considered, in the earlier correlation analyses, to have a robust embryologically plausible association with this herbicide category. In the case of cleft lip, elevated rates during a sprayed quarter were observed for only 4 of 12 sprayed counties at 3 quarter lag (when $r = .313$), while for "all anomalies" at 2 quarter lag, elevated rates were observed in only 2 of 12 sprayed counties. In the remaining sprayed counties (8 and 10 respectively) rates were actually lower at these times (Table E7). Clearly no temporal relationship is suggested.

Phenoxyherbicides: No embryologically plausible and statistically significant association was previously observed between birth defects and this herbicide category, although a significant elevation was noted for stillbirths at lag 0. In no instance did more than 7 out of 12 sprayed counties demonstrate higher rates of outcome during a sprayed period, at any of the lag intervals (Table E7).

Chlorinated Herbicides: These were used in only three counties, and provide insufficient data for comparison of mean rates. No clear pattern is suggested (Table E7).

Non-Chlorinated Herbicides: Only four counties were sprayed, insufficient for reliable comparison of mean rates, although no pattern is suggested (Table E7).

3.) Further Analyses of Spina Bifida and Cleft Lip (Combined Categories)

From a strict embryological standpoint, it may be illogical to have analysed spina bifida with and without hydrocephalus as if these were two discrete entities. There is no indication from the scientific literature that these should be viewed as separate conditions with distinct etiologies. Similarly, cleft lip with and without cleft palate are not considered fully plausible as discrete entities.

For these reasons, the entities "total spina bifida" and "total cleft lip" have also been analysed.*

Total Spina Bifida

Correlation coefficients were calculated for all 7 exposure categories across all four lag periods (Table E8). Of 28 coefficients, so calculated, one would expect one or two of these to be statistically significant at a probability of $p \leq .05$.* Random chance would also tend to produce a roughly equal number of positive and negative correlations. In actual fact, 10 were positive, 14 were negative, while the remainder were neutral ($r = .000$). Two

* Such analyses, based on greater numbers of cases, are statistically more powerful than the analyses of their respective subcategories.

significant coefficients were identified, one associating aminocarb exposure with total spina bifida at a lag of 3 quarters ($p \leq .05$), the other associating non-chlorinated herbicide exposure with this outcome at a lag of 2 quarters ($p \leq .01$). While such associations could have resulted from chance alone at this level of frequency,* the lag intervals themselves are considered embryologically plausible.

Comparison of mean rates across lag intervals was carried out for each county to further assess possible temporal association and plausibility (Table E9). The most plausible lag interval for total spina bifida is at 3 quarters, although a lag of 2 quarters is also possible. The greatest number of positive differences was, however, found at lag 0 (all exposure categories combined). The number of positive differences for lag 2 was never exclusively greater than at any other lag interval for any of the individual exposure categories. Although aminocarb had been significantly correlated with total spina bifida at lag 3, the mean rate of occurrence was higher at this lag interval in only two counties (fewer than observed for lags 0 and 1). While non-chlorinated herbicides had been significantly correlated with this outcome at a lag of 2 quarters, this correlation was based on only 6 paired values, and in only one county was there a positive difference in mean rates (true also of lags 0 and 1, while no positive county differences were seen for lag 3).

* The actual expected value at a probability of $\alpha = .05$, is 1.4 significant correlations.

Total Cleft Lip

A total of 28 correlation coefficients were calculated for this combined category (Table E10). Two were found to be significantly elevated ($p \leq .05$), whereas one or two (1.4) were expected on the basis of chance alone. Chance would also lead one to expect a roughly equal number of positive and negative correlations, while in fact 7 were positive, 12 negative and the remainder undefined. The two significant correlations are both positive and at embryologically plausible lag intervals (other forestry insecticides at lag 3, and at lag 4).

Comparison of mean rates across lag intervals revealed a total of 57 positive differences (Table E11). Sixteen of these (28%) were in lag 0 and are thus not considered embryologically plausible. Six, 17 and 18 were seen respectively at lags 1, 2 and 3. However, in the case of lags 2 and 3, 7 and 9 positive differences derive from the temporal association between fenitrothion and total cleft lip even though this chemical is highly negatively correlated with this outcome. Thus the two sets of findings are not mutually consistent. In reference to other forest insecticides for which significantly elevated correlation coefficients were previously described at lags 2 and 3, a total of only 4 and 5 positive differences are noted (although even fewer (2 and 3) are seen at lags 0 and 1). This finding does not contradict the correlation analysis, but certainly does not add much (if any) strength to the evidence of association.

Thus correlation and temporal analyses of the total cleft lip category fail to provide any consistent evidence of association with pesticides used in forestry that cannot be equally well explained by random variability.

PRINCIPAL FINDINGS (CONSOLIDATION)

Correlation analyses of discrete anomaly categories and subcategories revealed 19 statistically significant positive coefficients where approximately 14 would have been expected by chance. Only 10 of these coefficients correspond with lag periods following exposure which might be considered embryologically plausible, 5 in association with insecticides and 5 in association with herbicides. Robustness of the statistically significant insecticide correlation coefficients was judged adequate for further consideration in 4 instances and in the case of herbicides in 2 instances:

		<u>lag</u>
Fenitrothion	Anencephaly	2
	Spina bifida without Hydrocephalus	2
	"All Anomalies"	3
Other Insecticides	Renal Agenesis	2
Herbicides with any Phenoxy Component	"All Anomalies"	2
	Cleft Lip	3

None of these gained further support from the comparison of mean birth defect rates between sprayed and unsprayed periods at the appropriate lag interval.

Comparison of mean rates to assess temporal association revealed consistently higher rates of stillbirth at a one quarter lag following each of the three insecticide applications. No temporal association for any of the reproductive outcomes studied was observed in the case of herbicides with any

phenoxy component, nor for the phenoxy herbicides. Data for the other two herbicide categories were considered too limited for reliable assessment:

Temporal Associations - Comparison of Mean Rates

Fenitrothion	Stillbirths	$\frac{\text{lag}}{1}$
Aminocarb	Stillbirths	1
Other Insecticides	Stillbirths	1

Significance testing, using the sign test, revealed a total of 36 statistically significant differences in mean rates ($p \leq .05$) (Tables E12, E13, E14, E15). Only 14 were expected by chance alone on the basis of 280 tests performed. However, only 3 statistically significant positive differences were seen, while fully 33 significant values were in a negative direction. If one conservatively proposes that only 1 in 4 lag intervals in each set of spray-outcome analyses should, on average, result in a positive difference, then (given 14 expected significant values) one should expect by chance that 3.5 significant values should be positive. As noted, only 3 significantly positive directional differences were actually observed in 280 tests performed.

Two of the significantly positive differences were found for stillbirths at a lag of 1 quarter (Table E13), in reference to fenitrothion and "other insecticide" exposures. Although, as just acknowledged, these might be chance occurrences, their close proximity in terms of lag interval and type of reproductive problem adds some strength to the observations already made that these insecticide groups appear to be associated with stillbirths at a lag of 1 quarter. However, these observations are inconsistent with correlation

coefficients approaching zero, signifying no evidence of an exposure response relationship (Table E2)*.

The other statistically significant positive finding is for the category "all anomalies", at a lag of 3 quarters in reference to aminocarb exposure. However, this refers to a situation where only 8 of 15 counties showed a positive difference in mean values (zero differences being ignored in the analysis). In addition, there is a negative correlation coefficient here indicating no evidence of an exposure response relationship.

Further analyses of total spina bifida and total cleft lip were carried out, because of doubts that their respective subcategories can really be viewed as embryologically discrete entities.

Geographic correlation and comparison of mean rates across specified time intervals fail to provide mutually consistent evidence of association between any pesticide category and the occurrence of total spina bifida. Of two significantly elevated correlation coefficients, in one instance (aminocarb, lag 3) temporal association across counties was less frequent than at two of the three other lag intervals, while for the remaining significant correlation (non-chlorinated herbicides at lag 2), the number of observations was really too low for reliable assessment. Both significant coefficients could have occurred as a result of random variability.

In the case of total cleft lip, two significantly elevated correlations were detected, associating "other forestry insecticides" with this anomaly category at lags 2 and 3. However, comparison of mean rates across lag intervals did not add much (if any) strength to these observations which could

* In addition, it is notable that all health outcomes under study showed at least one significant correlation except premature (20-27 weeks gestation) livebirths. This finding further detracts from the evidence of a stillbirth effect because premature births would be expected to vary in accordance with stillbirth frequency.

be explained readily on the basis of multiple significance testing in the context of random variability.

INTERPRETATION

There can be no simple interpretation of these results when viewed in isolation from other relevant information including the results of case control studies presented in Section F of this report.

The critical importance of bias and confounding must be assessed with care. Bias can be defined as any process at any stage of inference which tends to produce results or conclusions that differ systematically from the truth. Confounding may be defined as the confusion of the effects of an extraneous variable with the effects of a study variable on the development of an outcome. In reference to both of these phenomena, one must be acutely aware of the potential for "ecological fallacy" (spurious associations). Such associations might easily have resulted from multiple correlation and significance testing. There is a very great likelihood of confounding from other factors. Such associations may in reality have no causal significance.

In reference to findings presented in this section, at most, it may be said that some statistically significant correlations and some indications of temporal association have been identified, but none of these provide strong or consistent evidence of a causal relationship. Geographic correlation analyses provide no evidence of causality, but do suggest a need to examine more closely the possibility of some relationship between herbicides with any phenoxy component to the category "all anomalies" and to cleft lip without cleft palate. However, it is considered doubtful whether the formation of this sub-category, by excluding cleft lip with cleft palate, is an embryologically sound concept.

Subsequent analysis of the combined category (total cleft lip) failed to reveal any such overall association. In the case of "all anomalies" one would have to postulate a "multiple effects" hypothesis in order to explain this association, in which case one would expect to see evidence of similar deviations in specific categories. Similarly, fenitrothion usage is significantly correlated with certain neural tube defect categories (anencephaly at lag 2, and spina bifida with hydrocephaly at lag 2). However, again one might question the embryological validity of differentiating spina bifida with and without hydrocephalus. Analysis of total spina bifida fails to reveal any such association. Fenitrothion is also significantly correlated with "all anomalies" at lag 3 requiring in this instance a multiple effects hypothesis.

All three insecticide categories analysed by comparison of mean rates are temporally associated with stillbirths at a lag of 1 quarter. Two of these temporal associations (fenitrothion and "other insecticides") were statistically significant. However, those observations are inconsistent with negative correlation coefficients signifying no evidence of an exposure response relationship. "Other insecticides" was also judged to be temporally associated with renal agenesis at this interval although this is not statistically significant, is not considered embryologically plausible, and the correlation coefficient is very low thereby demonstrating no evidence of an exposure response relationship. By contrast, while phenoxy herbicides and stillbirths are correlated significantly at a 0 quarter lag, comparison of mean rates does not confirm a consistent temporal pattern at this or any other lag interval.

Any one of these observations may be explained by random variations resulting from assessments having been performed on a large number of comparisons. It is also possible that such temporal association could derive from simultaneous cyclic patterns of both chemical usage and reproductive outcomes which may not be causally related. Criteria for assessment of causality must therefore be applied, not simply to the results of the analyses presented in this section, but to the full array of all information and analyses presented in earlier reports, and in subsequent sections of this report.

CONCLUSION

At this stage at least, based on the results of correlation analyses and comparisons of mean rates, it may be said that no evidence of any strong or consistent association between any particular forest pesticide and outcome category is apparent.

F. CASE CONTROL STUDIES

A case control study starts with identification of persons with the disease (or other outcome variable) of interest, and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or, alternatively, the quantitative levels of the attribute in each of the groups (Last 1983). Such a study can also be termed "retrospective" because the subjects are drawn according to their disease status (i.e., with or without) and then assessed for postulated antecedent causal factors.*

Case control studies differ from geographic correlation and temporal comparison studies (such as presented in Section E) in several important ways.

Case control studies are based on data that are linked at the level of individuals, while geographic studies link data at the level of geographic units and temporal studies aggregate data within units of time. In this way it may be assumed that if a case control study demonstrates an association between an independent and dependent variable (e.g., a documented exposure and a presumed outcome) then, by definition, one can be quite confident that persons with such an outcome are more likely to have such an exposure. This assumption cannot be made from the results of a geographic correlation study in which rates of a presumed outcome might vary among areas with different levels of a given exposure. An elevated correlation coefficient based on geographic units of analysis, does not imply that individuals with that outcome necessarily have a different level of exposure than those in whom the outcome is lacking. Similarly no such extrapolation can be made to individual exposure outcome association based on temporal comparisons of mean rates.

* A more complete description of study methods is included in Appendix III.

It is largely for the reasons just outlined that geographic and temporal studies tend to be used to generate hypotheses, at an earlier stage of a study. By contrast, case control studies are used more often in the hypothesis testing context. Case control studies are for these reasons closer to the principles of causal inference than are geographic and temporal studies. The results of case control studies should be accorded greater weight in the assessment of evidence.

Nonetheless, evidence from case control studies cannot, in isolation, establish causality. The problem still remains that even though cases and controls might differ consistently in reference to a given factor (e.g., chemical exposure), that difference, per se may not be the "cause".*

Case control studies have been undertaken by members of the Task Force, focussing on stillbirths, neural tube defects, facial clefts and renal agenesis, utilizing one or two distinct potential exposure periods - first trimester, and periconceptional.** These periods are defined in operational terms in the following subsection (Methods).

* The "prospective" study, characterizing individuals by exposure and measuring differential rates of outcome is conceptually closer than the case-control design to the notion of causality, although establishing a cause and effect relationship may still be elusive. Such prospective (or cohort) studies can be confounded by other differences between groups and among individuals. Prospective studies are often difficult and costly unless the outcome under study is frequent, and even if frequent even then can be done only if a suitable cohort of exposed persons can be identified.

The most rigorous epidemiologic evidence can be obtained only from a randomized controlled trial, in which such confounding factors are more likely to be randomly distributed between experimentally exposed and non-exposed groups. Evidence from a well conducted randomized trial is thus the strongest basis for establishing causality. A randomized trial would be unethical in the context of human exposure to chemicals, and for this reason toxicology studies are restricted to animals.

** While stillbirths are a fairly common reproductive outcome, a suitable prospective cohort of exposed pregnant women cannot be obtained. While the other adverse outcomes are much less common than stillbirths, again no suitable cohort can be readily obtained. The case control approach was therefore chosen as the most rigorous available method of studying whether or not an association exists between various pesticide exposures and these adverse reproductive outcomes.

Method

The choice of Stillbirths, Neural Tube Defects, Facial Clefts and Renal Agenesis, as relevant reproductive outcomes for particular study by the Task Force, has been explained elsewhere in the report (Section B).

Cases were identified from the Canadian Congenital Anomalies Surveillance System, while controls were identified (by Statistics Canada) from the Provincial Registry of Livebirths. Each case control study contains two controls for each case. One set of controls was chosen to match each case by date of birth and sex, while the second set of controls was matched by county and day of birth but chosen from an adjacent year. The first set of controls therefore fully exploits geographic variability (not matched for county of residence), while the second set (not matched for the same year of birth) exploits year to year variation (where applicable) in amount and area sprayed.

Municipality* of maternal residence at the time of birth was taken as an indicator of residence during the first trimester, and for each individual an "exposure window" was calculated. First trimester exposure was represented by the 15 week gestational period from 2 weeks prior to conception to 13 weeks following, a susceptible time period for birth anomalies.** An additional exposure "window" was also assessed for neural tube defects, namely a "periconceptional" exposure period from 2 weeks prior to 5 weeks following conception. Based on the residential address and these time "windows", exposure scores were assigned in a standard way, using the chemical data base (as described in Section D).

The following sample characteristics were obtained (Figure 7):

* There are approximately 5,000 municipalities (incorporated places).

** See Appendix III for details of exposure window calculations.

Figure 7 SAMPLE CHARACTERISTICS OF CASE CONTROL STUDIES

	SB ²	An ³	NTDs SB+H ³	SB-H ³	CP	FC CL	CL+P	RA
Cases	298	103	58	74	47	39	41	30
#1 Controls ¹	299	384						
#2 Controls ¹	302	386						

SB = stillbirth

NTD = neural tube defect

AN = anencephaly

SB+H = spina bifida with hydrocephalus

SB-H = spina bifida without hydrocephalus

RA = renal agenesis

FC = facial cleft

CP = cleft palate

CL = cleft lip

CL+P = cleft lip with
cleft palate

- 1 The same controls (both sets) were used in all case control analyses of birth defect categories. This is discussed in Appendix III.
- 2 The numbers of SB cases and controls were not exactly equal due to the deletion from the study of some women from other provinces.
- 3 The subcategories of NTD are not mutually exclusive, as 11 cases had two subcategories of defect. This situation always involved anencephaly plus another NTD subcategory.

To estimate the power of the stillbirth study, the minimum detectable relative risk was calculated assuming 295 cases, an equal number of controls and an exposure prevalence of 30% (based on the highest prevalence obtained). The relative risks detectable under these circumstances are a function of two probabilities: α , the probability of rejecting the null hypothesis when it is actually true, and β , the probability of accepting a null hypothesis (that there is no effect) when it is in fact incorrect. A minimum detectable relative risk of less than 2 can be achieved when α is .05 at all three levels of β (.05, .10, 0.2) as illustrated in figure 8. This compares reasonably well with many other studies in the environmental health field and gives some idea of the potential power of this study under these fixed assumptions.

Power decreases with deviation in either direction from a prevalence of 50% when sample size is held constant. Actual power achieved is therefore primarily a function of exposure prevalence, and can be estimated for each of the exposures actually examined in relation to cases and controls. The same power calculations hold for the category "major anomalies" but not for the individual anomalies.

Figure 8

Minimum detectable relative risk in an unmatched case-control study* for various levels of α , β

β	α (two-sided)		
	0.10	0.05	0.01
0.05	-	1.9	2.2
0.10	1.7	1.8	2.0
0.20	1.6	1.7	1.8

* Assumes 295 cases, an equal number of controls and a prevalence of exposure in the target population of 30%.

RESULTS

F.1 FIRST TRIMESTER EXPOSURE STUDIES

1. Stillbirths

The distribution of paternal and maternal ages, months and years of birth, and gestational age were compared between cases and the two sets of controls (Tables F1, F2.1, F2.2, F3, F4, F5.1, F5.2).

These distributions were subjected to Chi Square analyses. Maternal age distribution was significantly different between cases and controls ($P = .048$) due to relatively greater representation by both younger and older women, although a test for trend was not significant ($P = .443$) (Table F2.2). Otherwise all distributions were similar except for gestational age (Table F5.2) where (as expected) lower ages were recorded for stillbirths ($P = .0000$). The distribution of exposure scores for stillbirth cases and controls is presented in Table F6, for four chemical groups (fenitrothion, aminocarb, phenoxyherbicides and agricultural chemicals).

Fenitrothion exposures* among stillbirths (maternal exposures) were classified into five categories. Cases were compared with controls separately and combined using Chi Square analyses in reference to three categories of finite exposure (Tables F7, F8, F9). Risk ratios were calculated for each of the exposure categories. No evidence of association was detected.

A similar approach taken in reference to aminocarb and phenoxy herbicide exposures (Table F6) revealed that the large majority of cases and controls were not exposed to these chemicals during the critical gestational period. In the case of aminocarb it was found that, of 298 stillbirths only 3 (1%) were exposed while of a combined total of 602 controls, only 4 (0.7%) were exposed. All 4 exposed controls were to be found within the first control group (299) constituting 1.3% of this group. Analysis of phenoxyherbicide exposure revealed 18 individuals with a history of exposure, equally distributed among the same 3 groups (6 or 2% in each instance). Based on these findings, no

*See Section D pp 19-22 for Determination of Exposure Index

association between stillbirths and exposure to either aminocarb or phenoxyherbicide exposure can be demonstrated. Should any underlying association exist but fail to be detected due to the power limitations of these analyses, such association clearly could not contribute to the large majority of stillbirths which actually occur.

Agricultural chemical exposures were extrapolated as previously described (Section D) from land use patterns of counties. Cases and controls were analysed in several ways: standardized risk ratios (SRR)* by county across 3 broad exposure categories (Table F10), SRRs for 6 exposure categories across three different periods (1972-74, 1975-77, 1978-80) (Table F11), and assessment for statistical significance comparing cases and controls across 6 exposure categories (Tables F12.1, F12.2). No coherent pattern emerged from these analyses: risk ratios were almost equally distributed above and below 1.00, and there was only one statistically significant value in a direction implying a negative association between exposure and stillbirths. This finding is likely to be a chance variation, as there is no evidence of an exposure response relationship.

Several different analyses were undertaken to explore the potential for associations within various subcategories. These included, in reference to forest insecticides and herbicides, and agricultural exposures, stratification by northern and southern regions** of the province (Tables F13.1, F13.2, F13.3), by county (Table F14), gestational age (Tables F15.1, F15.2, F15.3) and

* For a discussion of the Standardized Risk Ratio (SRR): see Appendix III

** This classification is arbitrary and does not strictly represent north and south directions. An alternative nomenclature might be "upper" and "lower" New Brunswick (Figure 8).

2

1	Saint John
2	Charlotte
3	Sunbury
4	Queens
5	Kings
6	Albert
7	Westmorland
8	Kent
9	Northumberland
10	York
11	Carleton
12	Victoria
13	Madawaska
14	Restigouche
15	Gloucester

¹ Counties 1 to 8 are considered "south", 9-15 are considered "north"

2 Note that the numbering system used by the CCASS and referred to in the tables and figures in this report is not the same as that used by New Brunswick government departments.

NEW BRUNSWICK COUNTIES



Note: This numbering system is not the same as that used by New Brunswick government departments, but is that which has been used by CCASS and referred to in this report.

maternal age (Tables F16.1, F16.2, F16.3). No coherent pattern emerged, and there were only 2 statistically significant findings - significantly low risk ratios for Kent and Northumberland counties. No association between these exposures and stillbirth occurrence was therefore demonstrated at this level of analysis, although it is noted that the highest estimated relative risk was found for the gestational category 20-29 weeks in reference to the agricultural exposure "window" (not statistically significant).

2. Major Anomalies

Prior to conducting case control analyses on neural tube defects, facial clefts and renal agenesis, a study was made of all these conditions combined in order to exploit the larger numbers of cases available for this purpose. The statistical power of this combined analysis is of the same order of magnitude as outlined for the study of stillbirths (page 47 & 48). This approach necessarily assumes a "multiple effects" hypothesis, namely that: should a given exposure be teratogenic, the effect might be seen at several anatomic sites. Thus a total of 381 cases were compared with 384 and 386 individuals in the first and second set of controls respectively. These analyses, as in the examination of stillbirths, assessed evidence for association in reference to the Saint John River Basin, northern and southern counties, year and quarter of conception and gestational age category. The "exposure variables" used in reference to major anomalies (combined) were the broad categories: forest insecticide, forest herbicide, agricultural spray window, and phenoxy herbicides.

The results of these analyses are presented in the form of "standardized risk ratios" (SRR). This estimate of relative risk compares cases and controls

on the basis of the frequency with which conception and early pregnancy took place in proximity to a presumed exposure to forest insecticide, forest herbicide, agricultural chemicals and phenoxy-herbicides. The overall results for these analyses are presented in Tables F17.1, F17.2, F17.3, and F17.4. Each of these demonstrates no significant association between the broad categories of exposure and the occurrence of a "major anomaly". One statistically significant value is recorded, a significantly low risk in association with phenoxy herbicides when cases are compared with the second set of controls. This is viewed as a random variation without biological significance* (although it might be reasonably argued that this may be evidence of a negative association).

No coherent pattern of "major anomalies" emerged from a stratified analysis of cases and controls within the Saint John River Basin with those occurring elsewhere, taking into account direction of difference, evidence for an exposure response relationship, and random variability for any of the broad exposure categories (Tables F18, F19.1, F19.2). However, in the analysis of north south trend, the two significantly elevated SRRs are both at the highest level of postulated agricultural chemical exposure** in northern counties when compared with either control group (Table F21). While this too might be explained by random variation, there is at least some suggestion of a trend here which should not be immediately dismissed. No coherent pattern emerged from analysis of historical period, year or quarter of conception, or

* As a total of eighteen SRR values were tested for statistical significance, one significant value can be reasonably expected by chance alone at a probability of .05 (1 in 20 observations).

** Agricultural Chemical Exposure Opportunity Index (ACEO Index)

gestational age (Tables F22.1, F22.2, F22.3, F22.4, F22.5, F22.6, F22.7) in reference to agricultural chemicals, fenitrothion, forest insecticide or forest herbicide categories.

3. Neural Tube Defects

Neural tube defects were studied by the case control method within the following categories: anencephaly, spina bifida (total), spina bifida with hydrocephalus and spina bifida without hydrocephalus. Numbers of exposed were sufficient for analyses only in reference to fenitrothion and the ACEO Index. The statistical power of these analyses is necessarily lower than obtained in the studies of stillbirths and major anomalies (combined).

Anencephaly

The risk of anencephaly following exposure to fenitrothion in the first trimester (Table F23.1a) reveals one statistically significant finding - an elevated SRR (2.77) in the lower of two categories of exposure, when compared with the first control group. However, only a small and non-significant elevation is noted in reference to the second control, and in neither comparison is there evidence of a consistent exposure response relationship. In fact, the higher exposure category is associated with a lower level of risk (SRR) in both sets of comparisons. Stratification into northern and southern counties demonstrates that most of the noted SRR value in the lesser exposed group derives from the south, while only a weak overall trend exists in the north (Table F23.1b).

Risk of anencephaly following potential exposure to agricultural chemicals (ACEO Index) was also assessed (Tables F23.2a and b) and failed to demonstrate any evidence of an association. Specifically there were no significant elevations, and no evidence of a consistent exposure response relationship.

A curious general observation however is that, without exception, the lowest SRRs in each of these analyses were to be found in the category "Not Exposed (but in window)". This observation is difficult to interpret as the risk of anencephaly in this group would appear to be somewhat lower (although not significantly so) than that for unexposed persons not in the window (which was taken as the reference group) a group that is numerically the largest and for whom risk estimates should be most reliable.

Fenitrothion analyses were also stratified according to two gestational age categories (Table F23.3), location within or outside the Saint John River Basin (SJRB) counties (Table F23.4) and north-south distribution (Table F23.5). While neither gestation category could be considered at excess risk, a significantly low SRR (0.15) was found in those within the exposure window but without finite exposure. However, this in fact represents only 2 cases and cannot be considered a reliable estimate. Nonetheless, the overall SRR (0.45) for this category of exposure for both gestation categories combined (20 cases) is also significantly low when compared with both sets of controls combined. This, in turn, must be compared with the larger number of non-exposed individuals not in the exposure window (62 compared with 20) from which the reference value (1.00) for SRR estimates was obtained. The possibility of an association between fenitrothion exposure during the first trimester and anencephaly cannot therefore be altogether excluded although the evidence for

this would appear to be very weak.*

Location within the SJRB (Table F23.4) was found to be significantly associated with elevated SRR values in the lower of two (non-zero) fenitrothion exposure categories with a lower degree of non-significant elevation in the higher category. These observations are made on the first control comparison - data on the second comparison reveal a similar (but not significant) elevation in the lower of the two finite exposure categories, but a low risk (SRR = 0.61) associated with the higher exposure category.

Another seemingly paradoxical finding was observed when the anencephaly analysis for the agricultural chemical exposure opportunity index (ACEO Index) was stratified into northern and southern counties (Table F23.5). While no statistically significant levels of SRR were demonstrated, and apparent trends were not consistent with an exposure response relationship (e.g., the highest SRR was found in the lower of 2 exposure categories among northern county cases), nonetheless, the lowest SRRs were found among those within an exposure window but with a zero exposure estimate. This was not however the case when the analysis was stratified by residence in or out of the SJRB. The pattern in this instance can only be described as very haphazard (Table F23.6).

In conclusion therefore, in reference to anencephaly, the results from case control study must be considered somewhat contradictory. The number of statistically significant findings in itself is not unexpected given the number

* These somewhat contradictory findings increased the importance of focussing on a smaller exposure window thought to be more critical to the development of the central nervous system - presented later in this section. There is no readily available explanation for this finding. While a seasonal difference in rates of outcome might be plausible, it is also possible that the smaller potentially unexposed group could have distinct sociodemographic characteristics that could influence the risk of anencephalus.

of tests performed, and this could reflect simply chance variability. There is however, some suggestion of SRR trend across the three groups defined by fenitrothion and ACEO Index exposure within the first trimester exposure window. Whether this is of biological importance will depend on the results of similar analyses using a smaller, embryologically more precise, "periconceptual" exposure window (Section F.2, page 67).

Spina Bifida

The risk of spina bifida (with and/or without hydrocephalus) was assessed in reference to potential for fenitrothion and agricultural (ACEO Index) exposure in the first trimester.

No coherent pattern for total spina bifida was demonstrated in reference to fenitrothion (Table F24.1, F24.2a and b). SRR values appeared to be randomly distributed, none were statistically significant, and there was no evidence of an exposure response relationship. Assessment of overall risk in reference to potential agricultural chemical exposures in reference to either control group similarly failed to reveal any evidence of association.

Risk of spina bifida with hydrocephalus after exposure to fenitrothion in the first trimester, when separately examined (Tables F25.1, F25.2a and b) also failed to reveal evidence of association with either fenitrothion or potential agricultural exposures. Similar analyses of spina bifida without hydrocephalus also revealed no such evidence (Tables F26.1, F26.2a and b). These findings are perhaps not surprising when viewed in the light of no overall association with either exposure during the first trimester for all spina bifida combined.

Stratification of spina bifida with hydrocephalus by gestational age (Table F26.3a, b and c) left insufficient cases in the lower gestational group for useful analysis or interpretation, while inconsistent patterns of risk were revealed for spina bifida without hydrocephalus and spina bifida combined across the various categories of fenitrothion exposure. Similarly, stratification by SJRB revealed a haphazard pattern of risk (Tables F26.4a, b and c). The highest risk was found in the lowest of two-exposure groups not in the SJRB, while low levels of risk were found among several more highly exposed groups. Clearly there is no evidence of association here.

Analysis of spina bifida in reference to agricultural chemical exposure (ACEO Index) was carried out within two levels of stratification: SJRB (Table F26.5a, b and c), and north-south distribution (Tables F26.6a, b and c). The pattern in each of these can only be described as very haphazard, with highest risks more often than not associated with low or even zero exposure.

4. Facial Clefts

Facial clefts were studied by the case control method within the following categories: total cleft lip (cleft lip with or without cleft palate - 80 cases), cleft lip with cleft palate (41 cases), cleft lip without cleft palate (39 cases), and isolated cleft palate (47 cases). Analyses were carried out in reference to both control groups with regard to fenitrothion and potential agricultural chemical exposures (ACEO Index). Analyses for association with aminocarb or phenoxyherbicides were not possible in the case of facial cleft categories as insufficient numbers were exposed to these chemicals.

Results of overall SRR analyses (Tables F27.1 to F27.11) were assessed for direction, magnitude, statistical significance and evidence of exposure response relationship. No coherent pattern of association was identified for any category of facial cleft.

Stratified analyses for association between facial clefts and fenitrothion exposure by gestational period (Tables F27.12, F27.13) and SJRB residential status (Tables F27.14, F27.15) revealed a haphazard pattern of risk and no coherent evidence of association.

Similarly, stratification of agricultural exposure analyses failed to reveal coherent patterns within SJRB residential group and north-south distribution (Tables F27.16 to F27.20).

5. Renal Agenesis

Only 30 cases of renal agenesis have been identified during the period under investigation. The case control study relating to this condition was thus numerically very limited. As in previous analyses, numbers of potentially exposed cases were sufficient only to examine for possible association with fenitrothion and agricultural exposure.

Risk of renal agenesis following exposure to fenitrothion in the first trimester (Table F28.1) reveals one statistically significant finding - an elevated SRR in the lower of 2 exposure categories in reference to the first control group. An elevated SRR is also noted for the same exposure category when compared with the second set of controls, but this is not statistically significant. While the SRR calculated for the highest exposure is much lower in both sets of comparisons, and does not suggest evidence of an exposure response relationship, only 2 cases experienced such a potential exposure and this must be considered too few for any defence of reliability in

interpretation. The possibility of an association with fenitrothion must therefore remain open for further consideration.

Risk of renal agenesis after exposure to agricultural chemicals (ACEO Index) was also examined (Tables F28.2a and b). While all SRR estimates were somewhat elevated, there was no evidence of an exposure response relationship when compared with either of the control groups, and none of the values were statistically significant.

Further considerations of renal agenesis, because of its relative rarity and consequently small sample sizes for analysis, require caution in view of the inherently low statistical power of these analyses. Nonetheless, additional analyses were undertaken, stratified for gestational age (Table F28.3) SJRB residential status, and north-south distribution.

Only the older of the two gestational age categories included sufficient cases for analysis. In this instance the elevated SRR (not statistically significant) in association with "any" fenitrothion exposure was expected due to the earlier findings (Tables F28.1, F28.3). This non-significant trend was found within both SJRB strata (Table F28.4).

In reference to agricultural exposure (Table F28.5), a statistically significant SRR elevation (5.96) was found in the lower of two categories of finite exposure (ACEO Index), outside the watershed (SJRB). However, the higher category of exposure was associated with a lower risk in this situation, while within the watershed the unexposed (in window) had a higher SRR (1.45) than the most heavily exposed (1.10). This pattern cannot be considered coherent. Stratification by north-south distribution similarly reveals no evidence of a coherent pattern (Table F28.6). Summary analysis is suggestive of an inverse exposure response relationship here, although this is not statistically significant and should be considered random.

Consolidation of Findings

Key findings of these case-control analyses are now presented in point form:

- i) No overall association was detected between stillbirth and potential exposure to fenitrothion, aminocarb, phenoxyherbicides or agricultural chemicals (ACEO Index) during the first trimester of pregnancy.

It is noted that the highest estimated relative risk was found for the gestational category 20-29 weeks in reference to potential agricultural chemical exposure (ACEO Index), although this was not statistically significant.

- ii) A category entitled "major anomalies" comprising all neural tube defects, facial clefts and renal agenesis revealed no association with potential exposure to forest insecticides, forest herbicides, phenoxy herbicides or agricultural chemicals.

However, in the analyses of north-south trend, the two significantly elevated SRRs are both at the highest level of postulated agricultural chemical exposure (ACEO Index) in northern counties.

- iii) No clear evidence of association was detected between anencephaly and potential exposure to fenitrothion and agricultural chemicals during the first trimester.

Nonetheless there is some suggestion of a trend in risk across all exposure window categories for both fenitrothion and agricultural exposure. Whether this is of biological importance requires further attention to the results of similar analyses using a smaller, embryologically more precise, exposure window. (Section F.2)

- iv) No association with fenitrothion or potential agricultural exposures (ACEO Index) during the first trimester of pregnancy was demonstrated in reference to the overall risk of spina bifida, or for the sub-categories with and without hydrocephalus.
- v) No association was detected between any of the facial cleft categories examined (total cleft lip, cleft lip with cleft palate, cleft lip without cleft palate, and isolated cleft palate) and potential exposure to fenitrothion or agricultural chemicals (ACEO Index) during the first trimester of pregnancy.
- vi) Case control study of renal agenesis was limited due to small sample size (only 30 cases). Although no clear evidence of association was obtained between this anomaly group and potential exposure to fenitrothion or agricultural chemicals, the possibility of an association with fenitrothion was raised in view of a statistically significant SRR elevation in the lower of 2 exposure categories in reference to the first control group. This may warrant some further consideration.

F.2 CASE CONTROL STUDY OF NEURAL TUBE DEFECTS

USING A PERICONCEPTIONAL EXPOSURE WINDOW

Case control study of neural tube defects using the first trimester window yielded ambiguous results. Due to concern that, for this category of defects, the exposure period may have been too wide to detect risk during the critical period of organogenesis, it was decided to focus on a limited time interval specific to neural tube development. Thus, a periconceptional window was

defined for the period from 2 weeks prior to conception to 5 weeks following, and new exposure scores entered for this period for both cases and controls.

Results

Analyses of risk associated with various categories of exposure were carried out for all neural tube defects combined, anencephalus, spina bifida with and without hydrocephalus. As in previous analyses, results of these analyses were stratified by control group, gestation, SJRB and north-south groupings.

Neural Tube Defects (Combined)

Some suggestion of an exposure response trend was observed in reference to fenitrothion exposure at early ages of gestation (20-36 and 37-38 weeks), based on the first set of controls. However, this was not statistically significant and not supported in reference to the second set of controls (Table F29). Stratification by SJRB suggested a possible exposure response trend within the river basin, but this also was statistically not significant and contrasts with a haphazard pattern outside the valley (Table F30). Similarly no consistent pattern of association within northern and southern strata could be discerned (Table F31). Overall there would appear to be no acceptable evidence of association between fenitrothion and the broad category of neural tube defects (combined).

Analyses of risk in reference to the ACEO Index (potential agricultural chemical exposure) revealed a significantly high ($SRR = 3.32$) risk in the highest of two exposure categories for births of 37-38 week gestation, while a significantly low risk ($SRR = .19$) was noted for the 20-36 week gestation category unexposed but with exposure potential. These significant findings were restricted to the first set of control analyses.

While analyses using the second set of controls (Table F32) failed to reveal such elevated or statistically significant values, in every exposure-gestation category except one, where it was possible to calculate an SRR value, the value was greater than 1, while it was lower than 1 in all but 1 of 6 gestation categories not exposed but in the exposure window. Stratification by SJRB failed to reveal any coherent trend or statistically significant value (Table F33).

In the case of north-south stratified analyses (Table F34), several statistically significant values were noted: significant elevations in each of the two exposure categories overall, and within the north (but not south) stratum. In both north and south, higher SRR estimates were obtained for the lower of two exposure categories, although the SRR value for the higher category was also elevated.* Generally, this supports the existence of some association between neural tube defects and the agricultural exposure opportunity index.

Anencephalus

Some suggestion of a trend in risk associated with fenitrothion exposure was obtained (Table F35), but the pattern cannot be considered particularly coherent. The SRR was lower than expected in the "non-exposed but in window" category in the overall analysis, and within each of three gestational strata. The overall SRR for this category was significantly low. This in itself is an enigmatic result, but in each strata generally higher SRR estimates were observed for each of two categories of non-zero exposure. However, estimates of SRR for the gestational category 39+ weeks were, in fact, lower than 1 for all exposure categories. In the other two gestational categories the SRR values

* This type of pattern would appear to make satisfactory biological sense only if early fetal death were occurring in the high exposure category.

appeared to be elevated, but these estimates are not statistically significant and were based on very small numbers. Overall, the SRR associated with the two categories of finite exposure were only slightly elevated (1.34 and 1.10) the higher exposure being associated with the lower of the two SRR estimates. None of these findings can be viewed as strong or consistent evidence of association between anencephalus and fenitrothion exposure, and may simply be the result of random variability.

Stratified analyses reveal that a weak (non-significant) general trend between fenitrothion exposure and anencephalus is found within the SJRB and northern county strata (Tables F36 and F37). However, confidence intervals for these estimates are very wide and no clear conclusions can be drawn.

Risk of anencephalus was similarly assessed in reference to the agricultural exposure opportunity index (Table F38). Again, it cannot be said that there is a coherent pattern of results. Generally, low SRR estimates are evident for the "not exposed but in window" category, but so too (in the non-SJRB stratum) is the highest SRR estimate in the entire study (SRR = 8.32 Table F39). Such wide variation would appear to reflect the fact that numbers of observations in this category are very small indeed (e.g., the SRR 8.32 estimate is based on 1 case and 1 control). While two of the low SRR estimates are statistically significant (Saint John River Valley stratum and combined risks for SJRB strata) these are based on very small numbers of cases (3 and 4 respectively) and cannot be considered robust. By contrast, the numbers of cases in the finite exposure categories are much more adequate for analysis (as is the reference "not in window" category), but show no statistically significant elevations of risk. Non-significant elevation (SRR = 1.77) is noted in the highest exposure category within the SJRB and the highest risk estimate for a finite exposure category is located in the lower of two categories of finite exposure in the southern county stratum.

In sum, there would appear to be no coherent pattern of risk associating anencephaly with potential exposure to either fenitrothion or the agricultural exposure opportunity index.

Spina Bifida

Spina bifida was studied in reference to fenitrothion and agricultural chemical exposure opportunity. Both subcategories of this anomaly - with and without hydrocephalus - were analysed separately and combined.

Spina bifida with hydrocephalus was devoid of any suggestion of association with either type of exposure, overall or within any of the stratified analyses (Tables F41, F42, F43, F44, F45, F46).

Spina bifida without hydrocephalus revealed some evidence of elevated risk in several categories of exposure. In reference to fenitrothion, the pattern appeared to be fairly random although some weak trends are suggested (Table F47). Stratification by gestation revealed a non-significant elevation (SRR = 2.76) in association with the gestation period 20-36 weeks, but very low risk, in reference to longer gestation (Table F47). No evidence of risk could be discerned outside the SJRB, but within this stratum a non-significant trend was observed across exposure groups (Table F48). No consistent pattern could be seen in reference to northern and southern counties (Table F49).

Analysis of spina bifida without hydrocephalus in reference to the agricultural opportunity exposure index suggests an overall association with this neural tube sub-category. This association is apparent in the gestation group 20-36 weeks (not statistically significant) in the higher of two categories of finite exposure (SRR = 2.39) (Table F50). A non-statistically significant trend is noted within the SJRB stratum, where an SRR of 3.33 is observed in the highest exposure category (Table F51) and the odds ratio for

this stratified analysis is statistically significant ($P = .0102$). Similarly, a statistically significant odds ratio ($P = .0186$) is noted in reference to the analysis stratified by north-south distribution, and in which an SRR of 3.84 is observed in the higher of two finite exposure categories in northern counties (Table F52). This significant finding holds for both control analyses, although the SRR values are different (Control group 1, SRR = 5.53; Control group 2, SRR = 3.15) as one would expect (Table F53 and F54).

Thus it appears that there exists a statistically significant association between spina bifida without hydrocephalus and the agricultural chemical exposure opportunity index. This association is characterized by substantially elevated estimated risks in northern counties and within the Saint John River Basin. The overall association, adjusted for SJRB residence, is depicted in Figure 9.

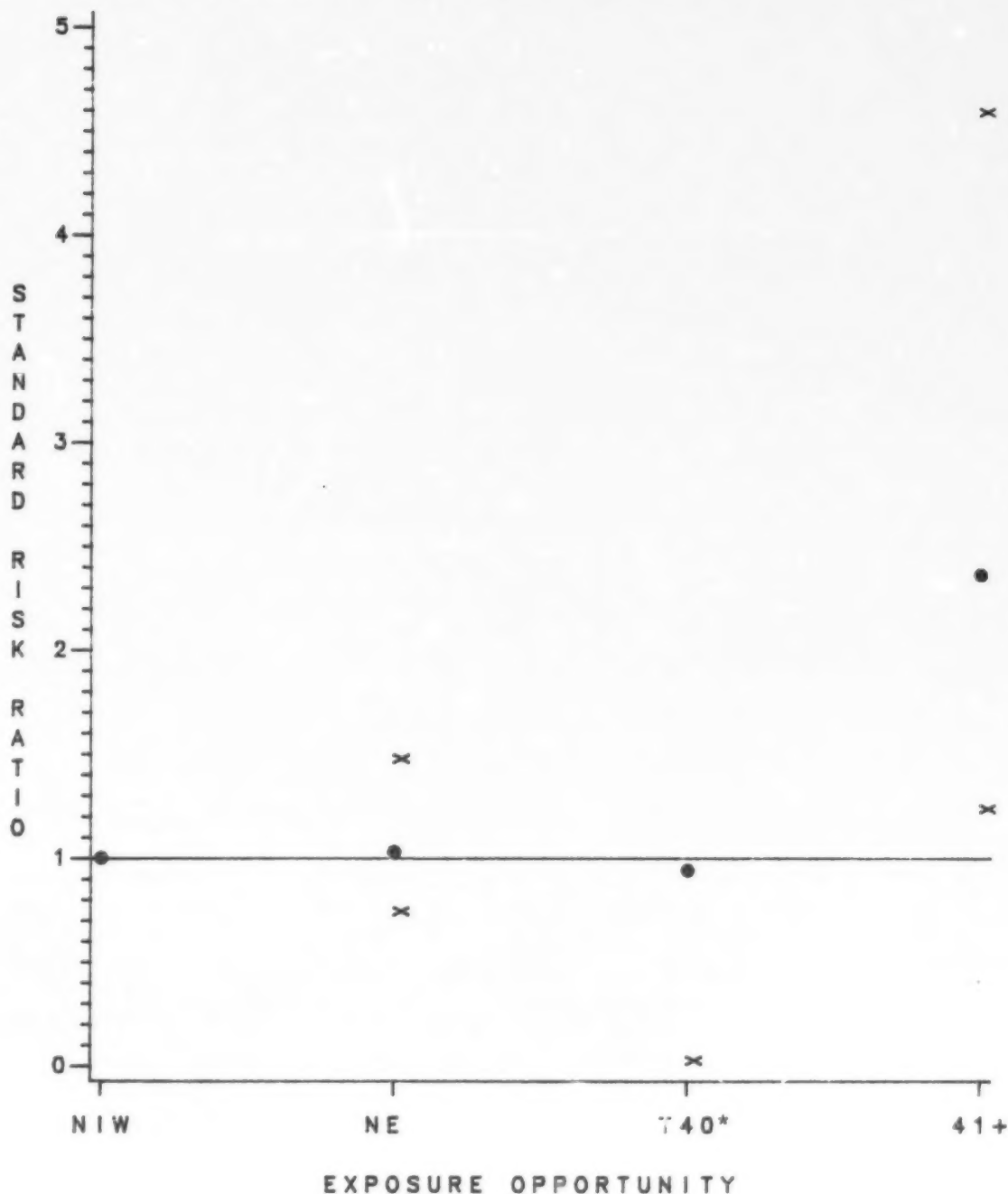
From a strict embryological standpoint, it may be illogical to consider spina bifida with and without hydrocephalus as if these were two discrete entities. An additional set of case control analyses was therefore carried out for the combined category of "all spina bifida". Available numbers of cases and controls were sufficient again to examine only for potential periconceptional exposure to fenitrothion and the Agricultural Chemical Exposure Opportunity Index. These analyses were stratified for gestational age, SJRB, and south-north county locations, as presented in tables F55.1 to F55.6.

No significant association was detected with "any" potential exposure to fenitrothion within any of the strata examined (Tables 55.1, 55.2, 55.3). Similarly, no evidence of association could be detected in relation to "any" potential exposure to the ACEO index (Tables 55.4, 55.5, 55.6). Lack of association was evident within both sets of control comparisons, although the data presented in the report are limited to the overall comparisons based on both sets of controls combined, for reasons of brevity.

FIGURE 9

-72A-

SPINA BIFIDA WITHOUT HYDROCEPHALUS AND ANY OPPORTUNITY
FOR EXPOSURE TO AGRICULTURAL CHEMICALS IN THE
PERICONCEPTUAL WINDOW, ADJUSTED FOR SJRB RESIDENCE



* T40 = Exposure Opportunity 1 to 40

CHISQ LINEAR TREND P-VALUE: 0.010

UPPER LIMIT ON CT. T40 IS 114.1

SJRB = ST. JOHN RIVER BASIN

X's denote the 95% confidence interval

While the statistically significant association between spina bifida without hydrocephalus and the agricultural chemical exposure opportunity index in northern counties and within the Saint John River Basin still stands, lack of any such association in reference to the combined category "all spina bifida" detracts from the plausibility of this association.

Consolidation

Periconceptional exposure to fenitrothion and potential agricultural chemical exposure (ACEO Index) were studied using case control analyses for all neural tube categories combined and individually. No coherent evidence of association emerged in reference to fenitrothion exposure in these analyses.

Some evidence of association was obtained for all neural tube categories combined and the ACEO Index. Examination of subcategories revealed a statistically significant association between spina bifida without hydrocephalus and this index of potential agricultural chemical exposure. This association is characterized by substantially elevated estimated risks in northern counties and within the Saint John River Basin. No association was demonstrated for the other two subcategories: anencephalus and spina bifida with hydrocephalus. Nor could any such association be demonstrated in reference to the combined category "all spina bifida".

F.3 SECOND TRIMESTER EXPOSURES AND STILLBIRTHS

All three insecticide categories analysed by comparison of mean rates were found to be temporally associated with stillbirths at a lag of 1 quarter (See Section E). However, those observations were inconsistent with negative correlation co-efficients signifying no evidence of an exposure response relationship. A lag of 1 quarter approximates a second trimester exposure model in reference to most stillbirths. A set of case control studies was constructed to examine whether or not potential chemical exposures during the second trimester were associated with the subsequent occurrence of stillbirths.

Analyses were carried out in reference to "any" chemical exposure (forest herbicide, forest insecticide and ACEO Index), forest herbicide, forest insecticide, fenitrothion, and the ACEO Index. Further subdivision was not statistically appropriate due to the insufficient numbers of cases and controls with potential exposure. In each exposure category, the analyses were stratified by maternal and paternal age, and geographic location in reference to south-north axis and in reference to the Saint John River Basin.

Analyses in reference to "any" chemical exposures revealed slightly elevated (i.e. 1.00) SRR's in virtually all strata. No statistically significant elevations were seen in reference to maternal age strata (Table 56.1), while stratification for paternal age (Table 56.2) revealed a marginally significant overall SRR elevation ($p=.05$:Mantel Haenszel Odds Ratio - adjusted for age). Both south and north strata (Table 56.3) suggested some degree of SRR elevation, as did the SJRB strata (Table 56.4), although in neither of these sets of analyses was there any statistically significant overall excess. Nonetheless, the fact that of all strata examined, only 1 (of 14) showed an SRR equal to or lower than 1.00 suggests the possibility of some underlying association.

Examination of similar stratified analyses in reference to forest herbicides demonstrated no evidence of a systematic elevation in SRR values (Tables 57.1 to 57.4). Although a few elevated values were noted, these appeared to be small in magnitude with no suggestion of statistical significance. Assessment of potential exposure to the broad category "forest insecticide" revealed generally small elevations in SRR (i.e. above 1.00), but in no individual strata and in no overall calculation was there evidence of statistical significance. It is noted that in this, as in the immediately preceeding analyses (Section F.2) the exposure measure was both categoric and general - any potential for exposure during a spray season being sufficient to classify an individual as having been "potentially exposed".

Sufficient numbers were available to examine potential fenitrothion exposure, using two categories of non-zero exposure in addition to the non exposure categories (NIW;NE)*. Seven of 15 counties demonstrated a risk of stillbirth greater than 1.00 (SRR) in association with any amount of potential fenitrothion exposure, while 7 demonstrated SRR values of less than 1, and one had a value of 1.00 (Table 59.1). This seemingly random distribution suggests no overall association between stillbirths and second trimester fenitrothion exposure when stratified by county, although it is clear that the number of cases per county is quite small for this level of stratification (15 strata). Stratification by gestational age, maternal age, paternal age, north-south residence, and SJRB (Tables 59.2 to 59.6) revealed no consistent patterns. Only two statistically significant values were observed, both of which were in reference to elevated SRR's in non-exposed individuals (paternal age 30+ and Mantel Haenszel Odds Ratio adjusted paternal age). There is accordingly no evidence of association between potential exposure to fenitrothion in the second trimester of pregnancy and subsequent occurrence of stillbirth.

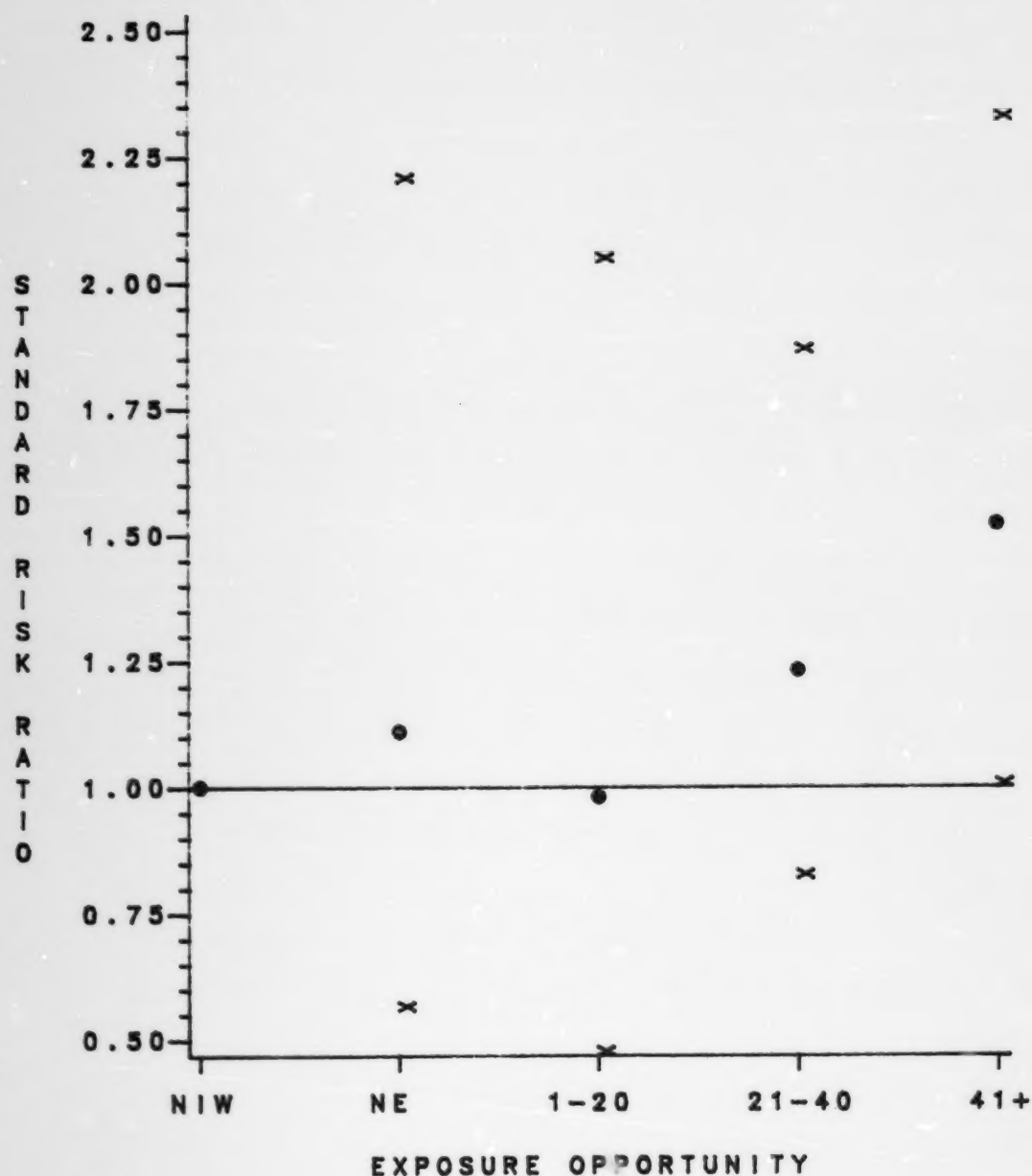
Finally, stratified analyses were carried out in reference to the ACEO Index. Six of 15 counties demonstrated SRR values greater than 1.00 (Table 60.1), 8 demonstrated lower values, while in one the SRR could not be calculated due to zero cells. There is also no evidence for a significant overall increase in risk (SRR 1.19). Maternal age was stratified and each strata examined across three categories of non-zero exposure (Table 60.2). Three statistically significant SRR elevations were noted: the highest exposure category was significantly elevated (SRR 1.67) within the maternal age group 20-29 years, while a significant elevation was also noted in the

*NIW = Not In Window; NE = Not Exposed, but in window. See Case Control Studies, Method (p. 52)

FIGURE 10

-75A-

RISK OF STILLBIRTH AFTER SECOND TRIMESTER EXPOSURE OPPORTUNITY TO AGRICULTURAL CHEMICALS ADJUSTED FOR MATERNAL AGE



M-H EXTENSION P-VALUE: 0.0332

intermediate exposure category (SRR 3.3) among those 30+ years. The Mantel Haenszel Odds Ratio for the highest exposure category, adjusted for maternal age, was also significantly elevated (SRR 1.52, $p=.05$). The M-H extension Chi-square, a test for trend, was statistically significant ($p < .0332$). The overall association adjusted for maternal age, is depicted in Figure 10.

Analysis of paternal age strata showed no statistically significant SRR elevations (Table 60.3) although a progressive increase in SRR value is noted in the age adjusted Mantel Haenszel Odds Ratio from lowest to highest ACEO Index category (Table 60.3). Analysis by gestational age strata (Table 60.4) reveals no clear evidence of concentration within either gestational age category. Analysis by north-south strata reveals a statistically significant SRR elevation in the highest exposure category in southern counties, although no evidence of elevation or trend in the north. Mantel Haenszel Odds Ratios, adjusting for north-south distribution reveals an increase in the Odds Ratio across exposure categories, but no statistically significant values overall (Table 60.5). Stratification by SJRB reveals generally increasing SRR values from low to high exposure categories within both strata, and in the strata adjusted Mantel Haenszel Odds Ratios, but no statistically significant values.

Consolidation:

Case control studies examined whether or not potential exposure to chemicals in the second trimester of pregnancy were associated with the occurrence of stillbirths.

Some overall suggestion of association was derived from analyses for "any" chemical exposure, but could not be explained by specific analysis of forest herbicides, forest insecticides, and fenitrothion exposures. No statistically significant values were located in these analyses.

However, stillbirths were found to be significantly associated with the Agriculture Chemical Exposure Opportunity Index. This association is evident at several stages of the analysis, and may underlie the initial suggestion of a weak association with "any" chemical exposure. Some evidence of an exposure-response gradient is apparent, although few of the SRR's are substantially elevated (most are in the order of about 1.5).

G. INTERPRETATION

Adequate interpretation of the findings of the Task Force in the context of the 4th term of reference requires recognition of the strengths and limitations of available information and the research strategy. A number of such features have already been described in the report, but it is important to recognize those and other constraints before reaching any conclusions. In addition, while the focus of the 4th term of reference is on evidence of association, the underlying question is whether there might exist cause and effect relationships. For this purpose, it is important to identify and apply a series of causal criteria. Scrutiny of our findings in the light of their limitations and with the application of causal criteria should advance knowledge in an objective way.

LIMITATIONS

The work of the Task Force had its origins in the public debate over the use of aerially applied insecticides in the forest industry. This debate can be characterized by two opposing viewpoints: opposition to the use of chemicals due to concern about possible adverse effects on people and the environment, and support for the use of chemicals in the interests of the forest products industry - a major contributor to the New Brunswick economy. The debate has received considerable media coverage, and the issue is of political importance.

While the job of the Task Force has been to develop and assess scientific information on the question of whether there is basis for concern about possible adverse human reproduction effects, it is recognized that this has been done in the context of a socio-political environment which cannot be

viewed as optimal for objective scientific enquiry. Evidence of bias can be identified on both sides of the issue, and has shown up in media coverage. The Task Force has at all times tried to keep itself free of any such bias, regardless of its source, in its purpose of arriving as close to the truth as possible within the limits of available data and the scientific method.

Nonetheless, many other limitations exist in this process and these are now broadly identified. The following comments are not intended to be all inclusive but serve to illustrate the scientific environment of our investigations.

The Hypothesis

The hypothesis for an association between forest insecticides and human reproductive outcomes was not based on established a priori evidence, but grew out of generalities such as the incorrect statement, carried in the media, that infant deaths from congenital anomalies were twice as common in New Brunswick as elsewhere in Canada. This erroneous statement was made in the context of coverage of the spruce budworm spray program. As documented in the Second Report, there is no evidence of any greater overall occurrence of birth defects in New Brunswick than in Canada generally. The 2-3 fold higher birth prevalence of neural tube defects in the province is a problem shared with other Atlantic provinces. This particular type of birth anomaly has been extensively studied and documented in the scientific literature. While there is good general evidence for environmental (as distinct from genetic) factors, no previous study has linked its occurrence to the use of insecticides and the prevalence was higher before spraying was introduced than subsequently.

Some prior evidence for a phenoxy herbicide - birth defect association does exist, and more clearly supports the further investigation into this in

the New Brunswick context. The content and quality of that evidence has been reported in detail in the Second Report.

The Absence of Alternative Hypotheses

In a truly free and open-ended scientific debate where there is no a priori evidence of an ill effect, it would be strictly logical to propose (as an equal and alternate hypothesis) that use of insecticides might be associated with a benefit to human health. The question was not posed in this way, although at least one other commission of enquiry - conducted by the Newfoundland Medical Society - made this point in view of the known ill effects on health of unemployment, and the fire hazard associated with dead forests. In the context of stillbirths, prematurity and neural tube defects, previous studies have demonstrated a relationship to poverty so that the plausibility of this alternative hypotheses is recognized.

This omission is pointed out, not with the intent of pursuing it, but for the sake of completing the logical framework. Similarly, one might hypothesize that neither effect may be associated with the proposed cause, or that both may, in fact, be true. In the latter instance the issue becomes "how much risk and how much benefit" or possibly "whose risk and whose benefit".

The lack of alternative hypotheses in this debate is considered a "limitation" in the sense that the Task Force has been asked to address itself solely to the issue of whether there is evidence of possible or real harm from the use of these chemicals. It will be up to the people of New Brunswick and their elected officials to consider the alternative hypotheses just stated.

Availability of Data

It has not been possible to study the occurrence of spontaneous abortion in relation to chemical use, or any other factor for that matter, since there

are no reliable data routinely collected on this. Such a study would have to be purposely designed to collect new information at considerably greater cost and time than available to the Task Force.

Data on birth anomalies also might be subject to ascertainment bias if physician and hospital recording practices were uneven throughout the province. This could include possible variance by population concentration and socio-economic status. These factors are known to vary within the province although their effect on ascertainment is not possible to judge. Furthermore, the number of cases of certain birth defects (e.g. renal agenesis) even after a decade of collection is still so small as to render the statistical analyses in reference to the insecticide spray hypotheses of questionable value.

Nonetheless, New Brunswick is one of only 5 provinces capable of addressing the issue of birth defect occurrence, having participated in the Canadian Congenital Anomalies System for well over a decade.* No other province east of Ontario has this capability although P.E.I. and Nova Scotia have recently joined the program.

Measurement

The problems of measurement placed the greatest limitation on the work of the Task Force.

By and large, measurement of outcomes was considered reliable and valid although even here difficulties arise. The problems of data availability (spontaneous abortion) and ascertainment variations (birth defects) have already been mentioned. In addition, there are the problems of a morphological

* The New Brunswick Department of Health is to be complimented for having the foresight to participate in this program. Despite the data limitations just acknowledged, few jurisdictions in the world currently offer the level of data development that was available to the Task Force.

classification which, by definition, focusses on visible defects and will miss non-clinically apparent, and non-visible defects. Similarly, the focus is on morphological anomalies identifiable at birth and long-term effects are not included. The classification used by CCASS is based on single defects and is not designed to identify syndromes. Severity is not fully assessed, although it may be implied by subcategories. For example, renal agenesis, in order to be ascertained, must be bilateral. Unilateral renal agenesis would not be identified as it normally asymptomatic. Subcategories such as spinal bifida with hydrocephalus necessarily identify a more severe clinical situation than spina bifida without hydrocephalus (assuming completeness in recording this diagnosis). However, with such categoric exceptions, there is no provision in this system for a severity assessment.

Other methodological problems arise from these measurement characteristics. For example, the system (CCASS) is based on the outcome of given pregnancies, and does not look to subsequent - second or third generation outcomes. This is an inherent problem in studying human populations which cannot be overcome at present. In animal studies, much shorter gestation periods and life spans are involved - although this introduces the difficulty of interspecies extrapolation (discussed in the Second Report). In addition, covariate information such as smoking or alcohol use during pregnancy, known to be associated with adverse reproductive outcomes, is not available and therefore cannot be taken into account in the analyses.

Despite these caveats, all of which place limitations on the study of birth outcomes in New Brunswick, the current system can be considered "state of the art" and does permit a wide variety of useful analyses, as has been demonstrated in the Task Force reports.

The greatest difficulties in measurement were encountered in the assessment of exposures. Although described elsewhere in this report (Section D), direct estimates of probable exposures were available in reference to the forest spray program. These data do not permit adjustment of individual scores for personal geographic mobility on a day to day or multiple residential/work station basis and so must be viewed as an "average" based on a fixed location, and may be quite inaccurate for given individuals. Furthermore there will have been, for some individuals, a change in residential address between the time of potential critical exposure (the "exposure window") and the time of delivery when residential address was recorded. Aerial drift was not taken into account for similar reasons - individual mobility, plus variations which must occur due to fluctuations in temperature, humidity, wind velocity, and spray technology. However, it is doubtful whether attempts to take these factors into account would be worthwhile given the mobility problem just outlined as a dominant factor. In addition, exposure and dose are not synonymous and no account is taken of type of work (which could involve occupational exposures).

For statistical analysis, it was necessary to group formulations without reference to additives or emulsifiers, and no account could be taken of variation in concentrations of impurities or accuracy of application. Spray intention records were adjusted for actual application, but the potential for errors in estimation or recording cannot be assessed.

Finally, for the purpose of studying birth outcomes, a short term exposure-outcome "model" was considered most plausible. However, the possibility of longer term accumulative effects cannot be ruled out, although

this is considered less plausible based on current knowledge. Similarly, our studies have focussed on maternal exposures although paternal exposures might also be of some importance - although in this instance there is no precedent.

Despite these limitations, the exposure information on forest chemicals compares favourably with the information available for the study of environmental health issues generally. Most certainly this information is far superior to that available on the use of chemicals in agriculture, a fact which must stand as a point of serious concern given the size and diversity of the agricultural industry in New Brunswick and elsewhere in Canada.

In the context of agriculture, no information is available for the 1970's that can be used to characterize actual use of chemicals or estimate resulting human exposures. For this reason, the Task Force was obliged to develop an Agricultural Chemical Exposure Opportunity Index (ACEO Index), based on information about agricultural land use patterns. This index is as close as we can come to the issue of agricultural chemicals in the context of our terms of reference. At the present time, more specific information would require more focussed field studies. However, the problems encountered illustrate the great need for a much better data base on agricultural chemical use in this province, and in Canada generally. The Task Force is, however, encouraged by some evidence of movement in this direction by the New Brunswick Department of the Environment (Section D).

Finally, some levels of data analysis required the formation of exposure categories which are essentially arbitrary. Inevitably, the reduction of continuous data (e.g., exposure scores) to categoric data involves a loss of information, although there is no way of circumventing this in certain types of analyses, in which the formation of categories is required (e.g., calculation of Standardized Risk Ratios).

Analysis and Interpretation

Great care has been taken throughout the report to caution the reader about the extensive use of correlation analyses and multiple testing for statistical significance. Such aspects of the report should be considered in the context of hypothesis searching, and a given likelihood (1 in 20) of chance associations must be accepted at the level of probability chosen ($\alpha = .05$). Only in the case control studies can it be claimed that we have actually tested hypotheses, and even here there must be great caution in attributing biological significance to findings which may be statistically significant. The converse has also been previously acknowledged - namely, failure to identify or confirm an hypotheses which might be true due to an inadequate scale of outcome or exposure measurement, or to insufficient sample size.

A more complete discussion of bias in analytic research has been published elsewhere (Sackett 1979). Defined as "any process at any stage of inference which tends to produce results or conclusions which differ systematically from the truth" (Murphy 1976) bias is an inherent risk of all such studies, and may occur at any stage of the research process: reading up on the field, specifying and selecting the study sample, executing the manoeuvre, measuring exposures and outcomes, analyzing the data, interpreting and publishing the results. The limitations and potential for bias in the present studies are therefore acknowledged as a prerequisite to the application of causal criteria in the following section of the report.

CAUSAL INFERENCE

Association between an outcome and a given exposure may be causal or non-causal. To assess the likelihood of an association being the result of a cause and effect relationship, it is useful to apply a series of criteria similar to those articulated by Hill in 1965. In various forms, such criteria are now widely applied to the problem of causal inference. The degree to which these criteria are met signifies the likelihood that the association is causal. The criteria used by the Task Force are as follows:

1. Time Relationship
2. Biological Plausibility
3. Biological Gradient
4. Consistency
5. Repeatability
6. Strength
7. Analogies
8. Specificity
9. Experimental Evidence

The meaning of these criteria, as applied in this report, are now described.

Time Relationship: In a causal association the presumed cause must precede the effect. This is an absolute criterion and has been applied in our studies by a series of time lagged analyses.

Biological Plausibility: There should be a biologically plausible basis for an association if it is causal. This criterion generally cannot be taken as an absolute as it depends on the biological knowledge of the day. However, in our studies, this has been applied most importantly to the issue of embryological plausibility, which, in the context of birth defects, is taken as an absolute criterion - given that the critical periods for organogenesis are exclusively in the first trimester.

Biological Gradient: This refers to evidence of a dose-response or exposure-response relationship, and is represented in our studies by two types of analyses. Correlation analyses assess evidence for a linear relationship between the amount of exposure and the rate of adverse reproductive outcome, while Standardized Risk Ratios have been calculated for various categories of increasing exposure.

Consistency: This is taken to refer to the agreement among the various studies undertaken by the Task Force. However, greatest weight is given to the results of case control analyses, as this study design is inherently more rigorous than the correlation analyses and comparisons of mean rates for reasons given earlier in the report (Section C, page 10).

Repeatability: This refers to the availability of supporting evidence from studies undertaken elsewhere. In the present context repeatability may be judged from the published literature.

Strength: This refers to the extent to which the presumed cause influences the effect, and is best represented by the calculation of Standardized Risk Ratios in the case control studies. Generally, given the limits of sample size and variability, risk ratios approaching or exceeding the value 2 would be considered substantial if statistically significant.

Analogies: By and large, as in the case of repeatability, this is judged by reference to the published literature. According to Hill "with the effects of thalidomide and rubella before us we would surely be ready to accept slighter but similar evidence with another drug or another viral disease in pregnancy".

Specificity: This refers to the extent to which a given association is specific to a particular chemical, a particular site or outcome, and a critical period. The greater the specificity, the more likely is the association causal.

Experimental Evidence: Direct experimental evidence is not available on human populations in this area of investigation. The reasons for this are primarily ethical. Some evidence from "natural experiments" has been assessed in the Second Report - such as the accident in Seveso, Italy - although this refers to the issue of dioxin contamination. The bulk of experimental evidence must be derived from toxicological studies in experimental animals and cell cultures, and has been taken into account in assessing causal inference.

These criteria as just explained are not identical to those proposed by Hill, but owe a debt to his general approach. They are now applied to the evidence of association presented in this report, in conjunction with evidence presented in earlier reports.

APPLICATION OF CAUSAL CRITERIA

Evidence for some degree of statistical association, whether causal or non-causal, has been derived from the three sets of analytical studies presented in this report. These are now listed:

Preliminary List of Associations

1. Fenitrothion and stillbirths at lag* 1.
2. Aminocarb and stillbirths at lag 1.
3. Other Insecticides and stillbirths at lag 1.
4. Fenitrothion and anencephaly at lag 2.
5. Fenitrothion and spina bifida without hydrocephalus, lag 2.
6. Fenitrothion and "all anomalies" at lag 3.
7. Other Insecticides and renal agenesis, lag 2.
8. Herbicides (any phenoxy) and all anomalies, lag 2.
9. Herbicides (any phenoxy) and cleft lip, lag 3.
10. ACEO Index and "major anomalies" in first trimester.

* All lags are in quarter years

11. ACEO Index and spina bifida without hydrocephalus.

- periconceptional exposure.

12. Fenitrothion and renal agenesis in first trimester.

13. ACEO Index and stillbirths in second trimester.

In the following matrix (Figure 11), each of these associations is identified by number and cross tabulated according to the type of evidence supporting the association:

A - evidence from case control study (either a significantly elevated SRR in an exposed category, or suggestive evidence of trend across ordered exposure categories);

B - significantly elevated correlation between amount sprayed and rate of outcome; and

C - comparison of mean rates.

These findings are arranged in this order to reflect the decreasing degree of rigour from A to C. Much greater weight should be accorded to evidence from case control studies (A) because only this type of study is based on the assessment of exposure and outcomes in the same individuals.

This tabulation reflects the degree of consistency obtained across the three different types of study.

FIGURE 11 MATRIX: ASSOCIATION AND TYPE OF EVIDENCE

ASSOCIATION	TYPE OF EVIDENCE		
	A	B	C
1	NO	NO	YES*
2	NO	NO	YES
3	NO	NO	YES*
4	NO	YES*	NO
5	NO	YES*	NO
6	NO	YES*	NO
7	Insufficient Data ¹	YES*	NO
8	Insufficient Data ¹	YES*	NO
9	Insufficient Data ¹	YES*	NO
10	YES*	Not Available ²	Not Available ²
11	YES*	Not Available ²	Not Available ²
12	YES*	NO ³	NO ³
13	YES*	Not Available ²	Not Available ²

* Statistically Significant ($P \leq .05$)

¹ Insufficient numbers of individuals with both these exposures and these anomalies could be located within the study period for useful analysis.

² It was not considered appropriate due to data limitations, to conduct an equivalent correlation or temporal analyses with the ACEO Index.

³ A first trimester or periconceptional exposure association is considered, for birth defects, compatible with a lag 2 or 3 correlation analysis, or a lag 2 or 3 comparison of mean rates.

As represented in this matrix, the only support for an association between chemical exposure and a given outcome at the level of individuals can be obtained from case control studies (type A) evidence. These implicate the Agricultural Chemical Exposure Opportunity Index in relation to "major anomalies" (a combined category) in the first trimester, to spina bifida without hydrocephalus in reference to periconceptional exposure, and to stillbirths in relation to second trimester exposure. A fourth associates

renal agenesis with fenitrothion exposure, but this is significant only in the lower of 2 exposure categories in reference to one of two control analyses, and is not supported by evidence from correlation or temporal analyses.

It was not appropriate to attempt correlation analyses or comparison of mean rates in reference to the ACEO Index due to data limitations. However, it should be noted that positive evidence from a case control study would take precedence over negative evidence from a geographic correlation analysis, or from comparison of mean rates. The corollary of this would hold that negative evidence from a case control analysis, which addresses association at the level of individuals, should carry more weight than positive results from these other forms of (aggregate) analyses.

Evidence for temporal association (based on comparison of mean rates) between the three categories of insecticide exposure and stillbirths at lag 1 is contradicted by negative correlation coefficients between exposure and outcome at the same lag interval. This ambiguous result should be discarded on the basis of case control studies which failed to show any evidence of association at an individual level. Similarly, the results of case control studies indicate no evidence of association of fenitrothion with anencephaly and spina bifida without hydrocephalus at lag 2, and with "all anomalies" at lag 3. This evidence, addressing exposure and outcome at the level of individuals, should discount the evidence obtained from the correlation analysis (type B), which was not supported anyway by comparison of mean rates.

The three remaining statistical associations (other insecticides with renal agenesis at lag 2, and phenoxy herbicides with "all anomalies at lag 2 and with cleft lip at lag 3) were based on significantly elevated correlations. Although not supported by comparison of mean rates (type C

evidence), in these instances case control studies were not carried out due to insufficient numbers of individuals with both these exposures and these outcomes for useful analysis. Thus, the possibility of an association at an individual level cannot be identified. However, it is also clear that the number of persons potentially exposed to these chemicals as used in the forest industry, at critical periods of pregnancy, is so few that there is virtually no potential for an adverse reproductive effect to occur during the study period, even if a causal relationship were to exist. Elevated correlation coefficients under these circumstances in New Brunswick should be considered statistical artifacts.

Based on the foregoing discussion the proposed associations (preliminary list) can be classified into three categories: probable, possible, and rejected - as indicated by the evidence at hand.

STATUS OF STATISTICAL ASSOCIATIONS

1. PROBABLE

- i. ACEO Index and "major anomalies" - first trimester
- ii. ACEO Index and spina bifida without hydrocephalus
- periconceptional exposure
- iii. ACEO Index and stillbirths - second trimester

2. POSSIBLE

- i. Fenitrothion and renal agenesis - first trimester

3. REJECTED

- All other statistical associations supported by only one of three types of evidence, and never supported by case control study.

The causal criteria previously outlined will now be applied to each of these associations.

1. ACEO Index and "major anomalies" in the first trimester

Time Relationship - a first trimester association is a plausible exposure-response period for birth anomalies.

Biological Plausibility - it is accepted that certain chemicals, some known and possibly many unknown, may induce birth defects.

Biological Gradient - in the analysis of north-south trend, the two significantly elevated Standardized Risk Ratios are both at the highest level of exposure in northern counties. This finding is the basis for our judgement that an association may exist, although apart from this extreme finding, there is no clear evidence of a dose or exposure-response relationship. In fact, the pattern of SRR values across the 7 exposure categories is quite haphazard.

Consistency - correlation analyses and comparisons of mean rates were not appropriate due to ACEO Index data limitations. However, earlier findings, presented in the Second Report, indicate a generally higher prevalence of birth defects in the Saint John River Valley and in northern counties, representing much of agricultural New Brunswick.

Repeatability - some evidence of association between agricultural chemicals and facial clefts has been demonstrated in the

literature (Gordon and Shy 1981). Neural tube defects have also been long associated with potato-producing areas (although the potato teratogen hypotheses is held in considerable doubt) (Emanuel 1972).

Strength - the evidence for association cannot be considered strong based on the SRR values. For the most highly exposed category these values are 1.08 and 1.07 in comparison with each of the control groups in southern counties, and represent no evidence of association at all. Values of 2.49 and 1.97 (both statistically significant) were found for the same exposure category in northern counties. These deserve attention and are accepted as evidence for association, but cannot be considered strong evidence.

Analogies - Most recently, a high relative risk for neural tube defects has been associated with nitrate concentration in ground water (Dorsch MM, Scragg RKR et al 1984). Nitrates are a major component of agricultural fertilizers.

Specificity - Neither the exposure index nor the outcome can be considered specific. Although the first trimester is specific to birth defects generally, the critical periods vary with the type of birth defect. This association cannot be considered specific.

Experimental Evidence - Major anomalies include neural tube defects, facial clefts and renal agenesis. Studies in experimental animals have shown 2,4,5-T to be capable of producing cleft palate and renal anomalies. This chemical (a phenoxy herbicide) is used in

agriculture. Other chemicals used in agriculture have also been shown to be teratogenic.

Thus, while an association between the ACEO Index and "major anomalies" has been demonstrated, this association lacks good evidence of a biological gradient, strength, and specificity. While it cannot, therefore, meet these important epidemiological criteria for causality, the association is considered biologically plausible in view of compatible experimental and epidemiological evidence. Thus, an underlying cause and effect relationship cannot be excluded.

ii. ACEO Index and Spina Bifida without Hydrocephalus -
Periconceptional Exposure

The same criteria applied to this association lead to somewhat better level of inference, although not sufficiently so to infer a necessary causal relationship between agricultural chemicals and this outcome.

Time Relationship - The periconceptional period of exposure, from 2 weeks prior to 5 weeks following conception, was chosen as the critical period for neural tube organogenesis. This is the best defined level of temporal association in our studies.

Biological Plausibility - The same order of biological plausibility applies in this instance as described for the preceding association. Lack of evidence of association from other neural tube defects (especially the combined category "all spina bifida") detracts from plausibility.

Biological Gradient - A statistically significant trend is noted across the exposure categories within both the SJRB stratum and in "northern" counties. This suggests the existence of an exposure-response relationship.

Consistency - As in the previous association, correlation analyses and comparisons of mean rates were not appropriate due to data limitations. However, a higher prevalence of neural tube defects in the Saint John River Basin and in northern counties has already been documented, and could be viewed as consistent with evidence of association in these areas. Lack of supporting evidence of association from other categories of neural tube defect detracts from evidence of consistency.

Repeatability - As previously noted, neural tube defects have previously been observed in association with potato growing areas of the world.

Strength - Substantially elevated SRRs were observed in the highest categories of exposure within the SJRB and "northern" counties (3.33 and 3.84 overall - both controls). This association is thus "stronger" than the previously discussed association (ACEO Index and "major anomalies", first trimester).

Analogies - The recently published association between water nitrates and neural tube defects (Dorsch MM, Scragg RKR et al 1984), stands as a particularly relevant analogy in this instance. Agricultural chemicals include nitrate fertilizers and spina bifida without hydrocephalus is a category of neural tube defect.

Specificity - In this instance, the outcome and the critical period of exposure are quite precise. Only the ACEO Index remains imprecise and renders the association to a low order of specificity.

Experimental Evidence - A number of chemicals have been demonstrated to induce one or more category of neural tube defect (exencephalus, anencephalus, spina bifida, hydrocephalus) in a variety of experimental animals (e.g. hamsters, mice, rabbits) (Lemire, Beckwith et al. 1978; Calter 1968). Such chemicals include antimetabolites, salicylates, excessive doses of vitamin A, and trypan blue.

Thus, it would appear in this instance that we have a moderately strong association between a specific outcome at a specific period of non-specific exposure. The biological plausibility of the association is limited by lack of evidence of similar association with any other separate or combined category of neural tube defect. The index itself is a surrogate measure, based on our extrapolation from land use and recommended chemical usage, and might represent some non-chemical characteristic of chemical use or some other phenomena occurring in agricultural areas during the same period. While a non-causal association cannot reasonably be excluded, the case for an underlying causal phenomenon clearly must be further investigated in New Brunswick, given the public health importance of neural tube defects. Both chemical (eg., waternitrates, trace elements etc.) and non-chemical (eg., cultural, nutritional, socioeconomic) hypotheses should be developed and further explored.

iii. ACEO Index and stillbirths in the second trimester

Time Relationship - A second trimester association is a plausible exposure response period for stillbirths.

Biological Plausibility - It is accepted that certain chemicals, some known and possibility many unknown, may induce stillbirths.

Biological Gradient - Statistically significant SRR elevations were found mainly in the highest of three exposure categories. Some strata, and all summary analyses, showed a progressive risk in SRR across exposure categories. These trends suggest a possible exposure-response gradient.

Consistency - Correlation analyses and comparisons of mean rates were not appropriate due to ACEO Index data limitations. However, findings presented in the Second Report indicate that only in reference to stillbirths and perinatal mortality does the reproductive health status of New Brunswick lag behind Canada, Nova Scotia and Quebec, although the difference is small.

Also in the Second Report, spectral analysis revealed a common, approximately annual stillbirth peak, in seven adjacent counties, six of which are within the Saint John River watershed area. As this river basin represents much of agricultural New Brunswick, these earlier observations add some consistency to the present association between stillbirths and the Agricultural Chemical Exposure Opportunity Index in the second trimester.

Repeatability - Few if any other case control studies of stillbirths have been carried out in reference to an index of potential agricultural chemical exposure.

Strength - All but one of the statistically significant SRR values are less than 2 (mostly around 1.5). Conventionally one would consider this to be evidence of a "weak" association although such a judgement should be tempered by the apparent biological gradient (noted above).

Analogies - Stillbirths are known to be associated with a number of chemical exposures, including cigarette smoking, fetal alcohol syndrome and some drug exposures.

Specificity - The ACEO Index is not a specific measure of chemical exposure; it is a surrogate for potential exposure to any agricultural chemicals(s). Stillbirth is normally viewed as a relatively non-specific birth outcome.* The second trimester is a broadly defined exposure period. The association therefore cannot be considered very specific.

Experimental Evidence - Stillbirths can be induced in experimental animals by exposure to a variety of chemicals.

Association between stillbirths and second trimester "exposure" to the ACEO Index is a biologically plausible finding. While the strength of the association appears relatively weak, some evidence of an exposure response gradient is apparent. This finding is consistent with earlier observations of an approximately annual cycle of occurrence identified in 7 counties, 6 of which are located in the Saint John River Basin, an agricultural belt. Despite these observations, the association cannot be judged to be very specific as the ACEO Index is only a surrogate estimate of potential exposure to agricultural chemicals, and stillbirths are not a single discrete entity.

*To illustrate the diversity within the stillbirth category, a three year review of etiologies was undertaken at the Grace Maternity Hospital in Halifax (1980-1982). Of a total of 106 stillbirths, the breakdown was as follows: fetal malnutrition 19, congenital anomalies 14, abruptio placenta 13, infections 7, toxemia 3, unexplained asphyxia 3, fetal hemorrhage 2, cord prolapse 1, isoimmunization 1, unexplained 43 (41%).

iv. Fenitrothion and Renal Agenesis - First Trimester

As previously noted, this possible association is suggested by a statistically significant elevated risk in the lower of 2 exposure categories in only one of two control studies. Although it gains no support from correlation analyses and comparison between mean rates, both of which produced no evidence for this association, an underlying association might still exist but fail to be detected due to small numbers. Clearly there is insufficient evidence here of a causal association and even the existence of a non-causal association may be questioned. Nonetheless, neither can be excluded due to the limited numbers of individuals both affected and exposed for analysis. The most that can be said is that, should an underlying association exist, it does not appear to be strong, and the potential for public health impact would have to be considered very small in light of the rarity of this condition.

CONSOLIDATION

A weak but significant association between the ACEO Index and major anomalies in reference to first trimester exposure was identified. A possible first trimester association between fenitrothion and renal agenesis is also recognized, although there is insufficient supporting evidence to assess this adequately. Even if there is an underlying causal association, the strength of the association would appear to be weak, the anomaly rare, and the potential impact very small.

The Agricultural Chemical Exposure Opportunity Index is significantly associated (during the periconceptional period) with the occurrence of spina bifida without hydrocephalus in the Saint John River Basin and "northern counties" of New Brunswick. This is not supported by evidence of association with the combined category "all spina bifida" or with the category spina bifida with hydrocephalus. The index itself is considered too non-specific to indicate a causal relationship to agricultural chemicals. Further hypotheses should be developed to explore specific chemical associations, related aspects of chemical use, and other plausible explanations unrelated to chemical use.

In view of the high prevalence of neural tube defects in New Brunswick and the association of the sub-category spina bifida without hydrocephalus with the ACEO Index at a critical period of embryonic development, there is a good case for further epidemiologic investigation.

The ACEO Index has also been found to be associated, in the context of potential exposure during the second trimester, with the subsequent occurrence of stillbirths. This is a weak but biologically plausible association, with some suggestion of an exposure response gradient. Earlier studies of the Task Force demonstrated a small but consistent excess of stillbirths in New Brunswick, with evidence of an approximately annual cycle in the Saint John River Basin. Clearly this finding also deserves continued attention.

H. CONCLUSIONS

1. Chemical Information

The quality and availability of information about chemicals used in our environment has been a central issue throughout the work of the Task Force. These concerns are focussed on policies and practices concerning the post-marketing use of federally approved products.

Much better quality of information has been documented in reference to the use of chemicals in forestry than in agriculture. The difference between the two industries is substantial. Specifically, the forestry industry has for many years maintained generally good records of the chemicals actually used including the time and location of their application. Equivalent quality of information has not been developed in the agricultural industry. While this industry is more complex, and has many more individual users, the fact remains that the variety of chemical use in agriculture is greater than in forestry and this industry poses greater potential for direct and indirect human exposure and improper use. Despite the complexity, adequate health and environmental protection would seem to require the development of an enhanced capacity for post-marketing surveillance of agricultural chemical use.

The current quality of information in agricultural chemical use precludes the conduct of epidemiological studies of reproductive problems, and indeed any other health outcome, in relation to specific chemicals or categories of chemicals. Instead, the Task Force has been obliged to develop its own general indicator of agricultural chemical use in order to address this issue in at least a general way. By contrast, information available on forestry chemical use has been sufficient for much more specific studies in reference to defined chemical groups.

These comments notwithstanding, the Task Force wishes to acknowledge the very real efforts made by the New Brunswick Department of Environment to improve the current quality and availability of information at the provincial level.

Availability of information comprises two components: is the information system capable of providing the data required for the purposes of health and environmental protection, and do existing policies support reasonable access to information from government and industry. Clearly, the absence of sufficient quality of information on agricultural chemical use constitutes an availability problem of the first type. However, it is also clear that existing policies have impaired access.

The problem of access to information, by and large, has not been encountered at the provincial level. However, as documented in the Second Report, the Task Force experienced considerable difficulty obtaining access to toxicologic evidence provided by pesticide manufacturers to Agriculture Canada, and in one instance was denied access to this information. To achieve efficient access, it became necessary to go outside Canada to obtain this information. Clearly, our current national policies and mechanisms (guided by Section 20, Schedule I, Access to Information Act) are not sufficient to provide reasonable access even to a government appointed inquiry without agreement from the manufacturer. The information was therefore sought in the United States, under the U.S. Freedom of Information Act, even though the original inquiry in Canada enlisted the direct involvement of the provincial Minister of Health. Much of the required information, requested from the U.S. Environmental Protection Agency, was received in March 1985, and additional information is expected.

2. Studies of Association

The major focus of this report has been the 4th term of reference:

To identify and examine any possible association between the use of chemicals in the environment and patterns of incidence of adverse human reproduction outcomes in New Brunswick, placing emphasis on the use of pesticides in the forest industry, but not to the exclusion of agricultural and domestic uses of chemicals.

- 2.1 No overall association was detected between stillbirth and potential exposure to fenitrothion, aminocarb, phenoxy herbicides or agricultural chemicals during the first trimester of pregnancy.

It is noted that the highest estimated relative risk was found for the gestational category 20-29 weeks in reference to potential agricultural chemical exposure (ACEO Index), although this was not statistically significant.

- 2.2 A category entitled "major anomalies" comprising all neural tube defects, facial clefts and renal agenesis revealed no association with potential exposure to forest insecticides, forest herbicides, phenoxy herbicides or agricultural chemicals.

However, in the analyses of north-south trend, the two significantly elevated SRRs are both at the highest level of postulated agricultural chemical exposure (ACEO Index) in northern counties.

- 2.3 No association was detected between any of the facial cleft categories examined (total cleft lip, cleft lip with cleft palate, cleft lip without cleft palate, and isolated cleft palate) and potential exposure to fenitrothion or agricultural chemicals during the first trimester of pregnancy.

- 2.4 No clear evidence of association was detected between anencephaly and potential exposure to fenitrothion or agricultural chemicals during the first trimester.
- 2.5 No association was detected between anencephaly and potential exposure to fenitrothion or agricultural chemicals (ACEO Index) during the embryologically more plausible periconceptual period.
- 2.6 Some evidence of association was obtained for all neural tube categories combined and potential agricultural chemical exposure (ACEO Index) during the periconceptual period.

Examination of subcategories revealed a fairly strong association between spina bifida without hydrocephalus and this index of potential agricultural chemical exposure.

This association is characterized by substantially elevated estimated risks in northern counties and within the Saint John River Basin. No association was demonstrated for the other two subcategories: anencephalus and spina bifida with hydrocephalus.

Analysis of the combined category "all spina bifida" failed to reveal any evidence of association with the ACEO Index during the periconceptual period.

- 2.7 Case control study of renal agenesis was limited due to small sample size (only 30 cases). Although no clear evidence of association was obtained between this anomaly group and potential exposure to fenitrothion or agricultural chemicals (ACEO Index), the possibility of an association with fenitrothion was raised in view of a statistically significant SRR elevation in the lower of 2 exposure categories in reference to the first control group during the periconceptual exposure period. This may warrant some further consideration.

2.8 Stillbirths were found to be significantly associated with second trimester exposure to the Agricultural Chemical Exposure Opportunity Index, and shows some evidence of an exposure response gradient. Few of the SRR's are substantially elevated (most are in the order of about 1.5).

3. Causal Inferences

The Agricultural Chemical Exposure Opportunity Index (ACEO Index) is associated with the occurrence of spina bifida without hydrocephalus in reference to periconceptional exposure in the Saint John River Basin and "northern counties" of New Brunswick. The index itself is considered too non-specific to establish a causal relationship to agricultural chemicals, and there is no evidence of an association with the combined category "all spina bifida" - which detracts from the plausibility of this association. Further hypotheses should be developed to explore specific chemical associations, related aspects of agricultural use, and other possible factors including nutrition, poverty and intergenerational factors.

A weak association between the ACEO Index and major anomalies was also identified and may reflect the underlying association with spina bifida without hydrocephalus. A tenuous association between fenitrothion and renal agenesis is recognized, although in this instance there is insufficient supporting evidence to assess this further. Even if an underlying causal association were to exist, the strength of the association would appear to be weak, the anomaly rare and the potential impact very small.

The ACEO Index is associated with stillbirths in reference to second trimester exposure. The association and shows some evidence of an exposure

response gradient. While the association is not very specific (because neither the ACEO Index nor stillbirth are discrete entities), it gains consistency from previous evidence of approximately annual cycles of stillbirths within Saint John River valley counties - where much of the agricultural industry is based. While there is insufficient evidence of a causal relationship, clearly there is a need to explore the association further.

In view of the high prevalence of neural tube defects in New Brunswick, the small excess of stillbirths in this province when compared with other parts of Canada, and their association with the ACEO Index at a plausible periods of embryonic development, there is a good case for further investigation into the occurrence of these adverse reproductive outcomes, with emphasis on agriculturally related hypotheses.

RECOMMENDATIONS: These are presented at the beginning of the report, immediately following the Summary.

REFERENCES

- Calter H. Teratology of the central nervous system. University of Chicago Press, 1968.
- Dorsch MM, Scragg RKR, McMichael AJ, Congenital malformations and maternal drinking water supply in rural South Australia; a case control study. Am J Epidemiol (1984) 119: 4, 473-486.
- Emanuel I. Non-tuberous neural-tube defects (letter). Lancet (1972): 879
- Gordon JE, Shy CM. Agricultural chemical use and congenital cleft lip and/or Palate. ArchEnvirHlth (1981) 35: 213-21.
- Hebda A, Jones GM. An Inventory of Agricultural Pesticide Usage in Prince Edward Island and Nova Scotia in 1982. Report prepared for EPS, Environment Canada 1983.
- Hill AB, The environment and disease: association or causation? Proc Roy Soc Med (1965) 58: 295-300
- Lemire RJ, Beckwith JB and Warkany J. Anencephaly. New York: Raven Press, 1978.
- Murphy EA. The logic of medicine. Johns Hopkins University Press Baltimore 1976.
- Ontario Weed Committee. Guide to Chemical Weed Control (1984), Ministry of Agriculture and Food, Ontario, publication 75.
- Ryerson RA, Tambay JL, Brown RJ, Murphy LA, McLaughlin B. A Timely and Accurate Potato Acreage Estimate from Landsat: Results of a demonstration Survey Methodology (1983) 9 (1): 119-138.
- Sackett DL. Bias in analytical research. J Chron Dis (1979) 32: 54-63.
- Shanks G. Pesticide Usage in New Brunswick (1980-82). Department of Environment, New Brunswick

APPENDIX I

CHEMICAL SPRAY DATA AND CROP INFORMATION EXTRACTED FOR
EXPOSURE - REPRODUCTIVE OUTCOME ANALYSES

INSECTICIDES^a

1. Fenitrothion in water
2. Fenitrothion in oil
3. Fenitrothion and Bacillus (BT)
4. Fenitrothion
5. Matacil]
6. Matacil] different formulations
7. Aminocarb in oil
8. Phosphamidin in water
9. Dimecron
10. Dimecron in water
11. Dylox
12. Dylox in water
13. Bacillus Thuringensis (BT) in water

HERBICIDES^b

14. Brushkill
15. Estern 3-3E
16. 2,4,5-T
17. 2,4,5-T with Estern 3-3E
18. Carbone
19. Desormone
20. 2,4-D
21. Weedone

- 22. Tordon
- 23. Roundup
- 24. Krenite
- 25. Dycier 10P
- 26. Herbet 20P

- a For insecticide analyses, numbers 1-4 were combined for all fenitrothion formulations; numbers 5-7 were combined for all aminocarb formulations and numbers 8-13 were combined as other formulations. Insecticide data units are kg active ingredient (AI)/county/year from 1971-1979.
- b For herbicide analyses, numbers 14-21 were combined as the chlorinated herbicides; number 22-26 were combined as the non-chlorinated herbicides. Herbicide data units are acres sprayed/county for the years

APPENDIX II

REPRODUCTIVE HEALTH ENDPOINTS OF INTEREST IN THE CHEMICAL EXPOSURE - OUTCOME ANALYSES

Congenital Anomalies^a

Group number	Name
1	Anencephaly
2	Spina bifida with hydrocephalus
3	Spina bifida without hydrocephalus
4	Cleft palate
5	Cleft lip
6	Cleft palate and cleft lip
7	Renal agenesis
8	All anomalies

Vital Statistics^b

9	Stillbirth
10	Premature birth (20-27 weeks gestation)

a Anomalies data are for the interval 1973-79 inclusive from the Canadian Congenital Anomalies Surveillance System. For a complete description, see relevant sections in the Task Force Interim Reports.

b Vital Statistics data are for the interval 1971-1981 inclusive. For a complete description, see relevant sections in the Task Force Interim Report.

APPENDIX III
CASE-CONTROL STUDY DESIGN AND ANALYSIS

Introduction

Case-control studies are carried out to determine whether there is an association between a proposed risk factor (such as a chemical applied to the environment) and an outcome (such as a congenital birth defect). Study subjects are chosen on the basis of their status with respect to the outcome under study (those affected are cases, those not affected are controls) and the tactic of "working backward" from effect to cause is used. In general, case-control studies are carried out in the following fashion:

1. A population-at-risk is defined for a given time period and geographical area (in this case, all live and stillbirths in New Brunswick from 1973 to 1979 are included). All cases of the outcome(s) of interest are sampled from this time - space window.
2. As each case is ascertained, the remainder of the population at risk (i.e., all non-cases) is sampled. (Naturally this was not done in real time in this study because all of the cases had already occurred but the concept is the same.) This is the control group. There is no single type of control group which is suitable for all studies and there are no firm criteria as to what constitutes an acceptable group. The particular way in which controls are selected in any study depends on the characteristics and source of the case series. In general, if the case series is population-based (as it is in this study), a random or stratified random

sample of the population will likely be a suitable control series (Breslow, Day 1980). The relative risk for a risk factor is defined as the ratio of the risk for those exposed to the risk for those not exposed, it is possible to obtain a consistent relatively accurate estimate of this relative risk from the case-control design in situations where the disease is rare (e.g. birth defects) (Howe, Choi 1983).

3. In order to determine whether any observed association between a risk factor and an outcome is direct, it is necessary to allow for other factors (such as gestational age) which might confound the association because they are related to both the risk factor and the outcome. Confounding effects can be controlled for in the design of the study (by choosing controls with the same value(s) of the confounding variable(s) as the cases) or in the analysis (by comparing only cases and controls which have the same range of values for the confounding factor(s)). The strategies used to deal with possible confounding in the present study are described below.

The Task Force Case-Control Studies

The Task Force (TF) case-control studies were carried out in two conceptually and operationally similar, but distinct phases. The first phase uses a one-in-three sample of New Brunswick stillbirths as cases and two liveborn controls per case. The second phase of the study uses as cases all infants registered with the Canadian Congenital Anomalies Surveillance System with at least one of the birth defects studied in the descriptive analyses. As in phase one, two liveborn controls were selected for each anomaly case.

The selection of stillbirth cases and all controls was carried out by the Vital Statistics and Disease Registries Section of Statistics Canada using the computerized New Brunswick live- and stillbirth records. The first control for each stillbirth and anomaly case series was matched to the case by date of birth only, otherwise the selection was random. The second control was matched by county of residence and day and month of birth from the previous year.

Although the two control series in each part of the study were matched to the extent just described, all major analyses were carried out disregarding the matching with either a pooled or stratified analysis. Strictly speaking, the date of birth (both control groups) and county matching (second control group) should be maintained in the analysis in order to obtain a consistent estimate of the relative risk but the bias introduced by ignoring the time matching is probably negligible (Greenland, Morgenstern, Thomas 1981).

Ignoring the county matching in the second control group creates more of a potential for bias. This match was made to control for possible (but unknown) confounding factors associated with county of residence. However, county matching inevitably matches to some extent on exposure and this could reduce the statistical power of any comparisons involving the second control group. In order to reduce this potential bias, controls in the second group were selected on the same date of birth in the previous year. Forest spray zones are moved from year to year, thus the potential matching on exposure would tend to be less for sprays involved in this program. However, agricultural spray locations change very little from year to year and the possibility of matching on exposure would tend to persist. For this reason, almost all analyses have been stratified by control group to allow any systematic differential in risk estimate from one control group to the other to be detected.

Statistical Measurements Presented in Task Force Tables

The statistical procedures used in these analyses are traditional ones appropriate for study designs in which stratification or "group matching" is used to balance the effect of confounding variables in the case and control groups. All case-control analyses in this report use approximate statistical methods for estimates, tests and confidence intervals. These approximate methods have been shown to be, "more than accurate enough in most practical situations" (Breslow, Day 1980). More complex exact and multivariate methods are available (although stratification on two or more variables is a basic form of multivariate analysis) but do not seem to be justified given the largely negative results of the stratified analyses and the small number of covariates that are available from the vital statistical records.

The following section gives a brief guide to the interpretation of elements of the statistical tables supporting the case-control section of the report.

1. The standardized risk ratio (SRR), which is also known as the odds ratio (OR), is an important component of the analysis because it approximates to the relative risk. The null (no effect) value of the SRR is 1.0. Values larger than 1 imply an increased risk and values lower than 1 suggest a decreased risk. For example, an SRR of 2.2 indicates an excess risk of 2.2 times or 120 percent higher than expected. Note that the referent category in each table (i.e., the exposure group that all others are compared to) has, by definition, an SRR of 1.0. Each exposure category has its own SRR as compared to the (no exposure) referent.

2. Confidence limits on the SRRs are often presented. It must be remembered that the SRR is a statistical estimate, the precision of which depends not only on the total number of cases and controls but also on their distribution in the exposed and unexposed categories. Most of the limits reported on the SRRs are calculated by an iterative method attributed to Cornfield (4). However, this technique is less satisfactory with small numbers and in some instances, limits are calculated using the test-based method of Miettinen (1976). All confidence limits in this report are at the 95% level, i.e., a null hypothesis corresponding to any SRR value falling outside a 95% confidence interval would be rejected at the 0.05 level of confidence.
3. Standard chi-square tests for association in a 2x2 table are calculated in all exposure category vs referent comparisons and provide a test of the null hypothesis that the SRR = 1.0 (i.e., that there is no effect of that level of exposure on the outcome). In fact, two such chi-squares are computed. A continuity corrected chi-square is reported in the tables with its associated p-value (level of significance). An uncorrected chi-square is also computed for use in the calculation of the test-based confidence limit on the corresponding SRR.
4. Most analyses in this report involved a risk factor with more than 2 levels of exposure. (Exceptions are the analyses involving dichotomous "exposure windows".) The usual analytical approach is to compare each exposure level to a referent category (see Sections 2 and 3 above) but it is also helpful to have an overall test of the null hypothesis that all of the SRRs are simultaneously equal to 1.0 (i.e., that there is no overall

effect of exposure on outcome). The statistic that is used is the usual one for testing homogeneity in k proportions (where k = the number of exposure categories) and is due to Armitage (1966). This statistic is reported as the "global test for homogeneity" and is given with its degrees of freedom and p -value.

5. When the exposure levels of the risk factor can be ordered (as in all of these analyses), the overall test of association described in (4) can be extended by testing for a trend in disease risk with increasing levels of exposure. The chi-square test which is used is also due to Armitage (1955) and is reported as the "test for trend" with its degrees of freedom and p -value.

Any or all of the statistics described in (2) to (5) might be included in any table of results (although all have been calculated) depending on the construction of the table. SRRs are always reported with some indication of their level of significance.

An unstratified analysis results in a single table of the statistics (1) to (5). A stratified analysis (i.e., one in which the cases and controls are partitioned according to levels of the covariate) results in as many such tables as there are strata plus two others.

The first of these latter two tables is the "crude" or "unadjusted" analysis. This analysis, which also produces all of the statistics (1) to (5), ignores the stratification and provides a reference, from its SRRs, of the form of the exposure-outcome relationship over the whole range of the covariate(s) of interest.

The second Table is the "adjusted" or "summary" analysis. Each of the stratum-specific analyses can be thought of as representing the effect of exposure on the risk of the outcome when the (joint) effect(s) of the stratification variable(s) has been held constant. If the SRRs are relatively constant across subgroups, they can be meaningfully combined to form a summary or "adjusted" estimate. The method which is used in this report is due to Mantel and Haenszel (1959) and is reported as the Mantel-Haenszel OR (Odds Ratio). This estimate is a weighted average of the subgroup-specific SRRs in the particular exposure category. The 95% confidence limits on this OR are test-based limits. The Mantel-Haenszel formula gives a robust and useful estimate of the common odds ratio even with large numbers of strata with sparse data (1).

The summary analysis also includes a test for linear trend due to Mantel (1963) and is reported as the "M-H extension". It is comparable to the crude and stratum-specific trend tests but is adjusted for confounding.

REFERENCES TO APPENDIX III

- Armitage P. The chi-square test for heterogeneity of proportions, after adjustment for stratification. J Roy Statist Soc, (1966), B 28: 150-163.
- Armitage P. Tests for linear trends in proportions and frequencies. Biometrics, (1955), II: 375-386.
- Breslow NE, Day NE, Statistical Methods in Cancer Research Volume 1 - The analysis of case-control studies. IARC Scientific Publications, (1980) No. 32, International Agency for Research on Cancer, Lyon.
- Cornfield J. A Statistical Problem Arising from Retrospective Studies. In: Proc 3rd Berkeley Symp Mathern Stat Prob IV. J Neyman (ed) pp 135-148, Berkeley: U Calif Press, 1956.
- Greenland S, Morgenstern H, THOMAS DC. Considerations in determining matching criteria and stratum sizes for case-control studies. Int J Epidemiol, (1981), 10(4): 389-392.
- Howe GR, Choi BCK. Methodological issues in case-control studies: Validity and power of various design/analysis strategies. Int J Epidemiol, (1983), 12(2): 238-245.
- Mantel N, Chit-square tests with one degree of freedom; extensions of the Mantel-Haenszel procedure. Am Stat Assoc J, (1963), 58: 690-700.

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst., (1959), 22: 719-748.

Miettinen O. Estimability and estimation in case-referent studies. Amer J Epidemiol, (1976), 103: 226-235.

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THE USE OF CHEMICALS IN THE ENVIRONMENT AND PATTERNS
OF REPRODUCTIVE OUTCOMES IN NEW BRUNSWICK

FINAL REPORT

I.

TABLES

Compendium of Abbreviations

Any	Any Exposure
CL	Confidence Limit
df	Degrees of Freedom
f	Frequency distribution
ha	Hectares
kg	Kilograms
M-H	Mantel Haenszel extension χ^2 analysis
n	number
NDA	No Data Available
NE	Not Exposed (See O)
NIW	Not in Exposure Window
O	In Window but not exposed (same as NE)
OR	Odds Ratio
p	Probability
r	Correlation Coefficient
SJRB	Saint John River Basin
χ^2	Chi-Square value

Notes

1. SRR and OR calculations of "risk" are based on case control studies and do not imply prospective or predictive information.
2. Method of assigning chemical exposure scores is described in Section D.
3. As explained in Section D of the report "windows" are the critical periods of organogenesis or fetal development (e.g., first trimester, peri-conceptional) during which a teratogenic effect would be considered embryologically plausible.
4. Some tables (e.g., F13-2) refer to north and south counties. This geographic distinction is outlined in Figure 8 (pages 56a and b). County codes used by CCASS are also noted in Figure 8.

TABLE D1: Estimates of Pesticide Usage Patterns in New Brunswick

CROP	ADJACENT PROVINCES		NEW BRUNSWICK		
	NS ^a kg/ha	PEI ^a kg/ha	NB ^b PERMITS kg/ha	CROP GUIDE ^c kg/ha	PREDICTOR ^d kg/ha
1. INSECTICIDES					
Potato	0.5	5.0	0.6	6.2	2.0
Tobacco	0.6	3.0			1.8
Strawberry	0.2	1.6	0.2	13.8	0.7
Grain			0.9	10.8	0.9
Vegetable	0.7	4.9	0.4	30.3	2.0
2. HERBICIDES:					
Potato	0.6	2.4	3.2	11.4	2.1
Tobacco	6.4	4.4		0.6	5.4
Strawberry	1.8	2.7	1.4	0.2	2
Grain	0.6	0.3	7.9		2.9
Vegetable	2.4	2	1.9	0.7	2.1
3. FUNGICIDES:					
Potato	1.4	20.3	9.2	7.4	10.3
Tobacco	34.6	9.5			22.1
Strawberry	79.6	7.1	7.2	3.2	7.2
Grain			0.008		0.008
Vegetable	0.5	1.7	2.8	6.2	1.7

^a Pesticide usage patterns supplied by Environment Canada

^b Based on pesticide permits as presented in the Second Report.

^c Based on Canadian Crop Guide, as presented in the Second Report.

^d The "Predictor" is the arithmetic average of ^a and ^b, except for the Strawberry Fungicide N.S. figure, which was deleted from the calculation.

Table E1

Pearson correlation between health outcome rate and exposure in all counties when spraying occurred from 1973 - 81^a, Lag = 0 quarters

OUTCOME	PESTICIDE GROUP ^b						
	INSECTICIDES			HERBICIDES			
	1	2	3	4	5	6	7
Anencephaly	.017	-.242	.070	-.075	-.020	.000	.793*
SB with hydrocephalus	.078	.006	-.134	.095	.167	.000	.942*
SB without hydrocephalus	-.014	-.098	.043	.002	.024	.000	-.218
Cleft palate	-.092	.035	-.094	.350	.374*	-.418	-.238
Cleft lip	-.121	-.056	.007	-.016	.019	.496	-.218
Cleft palate with cleft lip	-.052	-.018	.032	.373*	.277	.000	-.343
Renal agenesis	.000	.354	-.076	-.192	-.199	.000	-.218
All anomalies	-.065	-.042	-.012	.378*	.409*	.406	.434
n for anomalies ^c	85	33	41	32	32	8	7
Stillbirth	.073	-.185	-.132	.539*	.596*	.345	-.018
Preterm birth	.109	.104	.039	.031	.054	-.391	-.051
n for births ^c	141	35	41	54	54	12	16

^a For specific time periods, see Appendices I, II

^b 1 = fenitrothion formulations, 2 = aminocarb formulations, 3 = other insecticides, 4 = herbicides with any phenoxy component, 5 = phenoxy herbicides, 6 = chlorinated herbicides, 7 = non-chlorinated herbicides

^c Number of paired data points on which the correlation is based for anomalies, still and preterm births, respectively. This is determined by the number of county quarters sprayed. For degrees of freedom, subtract 2.

* = nominally significant at $p \leq 0.05$.

Table E2

Pearson correlation between health outcome rate and exposure in all counties when spraying occurred from 1973 - 81^a, Lag = 1 quarter

OUTCOME	PESTICIDE GROUP ^b						
	INSECTICIDES				HERBICIDES		
	1	2	3	4	5	6	7
Anencephaly	.067	.214	.144	.215	.256	.000	-.187
SB with hydrocephalus	.073	.384*	-.106	-.107	-.099	.219	.000
SB without hydrocephalus	.082	-.224	.193	.048	.111	.000	.000
Cleft palate	.020	-.094	.026	-.108	-.098	.000	.000
Cleft lip	-.079	-.121	.026	-.220	-.238	.000	.000
Cleft palate with cleft lip	.037	.034	-.018	-.157	-.155	-.257	.000
Renal agenesis	.188	-.174	.055	.236	.274	.000	-.238
All anomalies	.075	.055	.116	.126	.145	.437	-.458
n for anomalies ^c	85	33	41	32	32	8	7
Stillbirth	.028	.009	-.133	.162	.172	.413	.059
Preterm birth	.009	.089	.094	-.092	-.104	-.192	-.494
n for births ^c	141	35	41	54	54	12	16

^a For specific time periods, see Appendices I, II

^b 1 = fenitrothion formulations, 2 = aminocarb formulations, 3 = other insecticides, 4 = herbicides with any phenoxy component, 5 = phenoxy herbicides, 6 = chlorinated herbicides, 7 = non-chlorinated herbicides

^c Number of paired data points on which the correlation is based for anomalies, still and preterm births, respectively. This is determined by the number of county quarters sprayed. For degrees of freedom, subtract 2.

* nominally significant at $p \leq 0.05$

Table E3

Pearson correlation between health outcome rate and exposure in all counties when spraying occurred from 1973 - 81^a, Lag = 2 quarters

OUTCOME	PESTICIDE GROUP ^b						
	INSECTICIDES			HERBICIDES			
	1	2	3	4	5	6	7
Anencephaly	.211*	-.106	.069	.103	.185	.313	-.269
SB with hydrocephalus	.031	-.034	.101	-.066	-.045	.000	.000
SB without hydrocephalus	.306*	-.149	.031	.337	.387	.313	-.078
Cleft palate	.014	.020	-.128	.631*	.443*	-.497	-.400
Cleft lip	.068	.583*	-.183	-.053	-.029	.000	-.269
Cleft palate with cleft lip	-.110	.178	-.206	-.117	-.095	.000	.000
Renal agenesis	-.066	-.023	-.364*	.144	.209	.000	.000
All anomalies	.175	-.022	.217	.485*	.437*	-.189	.037
n for anomalies ^c	85	33	41	25	25	6	6
Stillbirth	.049	-.132	.286	-.013	-.043	-.372	-.082
Preterm birth	.040	.133	.202	.131	.121	-.312	-.099
n for births ^c	141	35	41	42	42	10	4

^a For specific time periods, see Appendices I, II

^b 1 = fenitrothion formulations, 2 = aminocarb formulations, 3 = other insecticides, 4 = herbicides with any phenoxy component, 5 = phenoxy herbicides, 6 = chlorinated herbicides, 7 = non-chlorinated herbicides

^c Number of paired data points on which the correlation is based for anomalies, still and preterm births, respectively. This is determined by the number of county quarters sprayed. For degrees of freedom, subtract 2.

* nominally significant at $p \leq 0.05$

Table E4

Pearson correlation between health outcome rate and exposure in all counties when spraying occurred from 1973 - 81^a, Lag = 3 quarters

OUTCOME	PESTICIDE GROUP ^b						
	INSECTICIDES			HERBICIDES			
	1	2	3	4	5	6	7
Anencephaly	.045	-.339	.116	.204	.297	.000	.000
SB with hydrocephalus	.139	-.170	-.072	-.160	-.161	.000	-.061
SB without hydrocephalus	.079	.025	-.117	-.115	-.128	.000	-.269
Cleft palate	.090	.253	-.128	-.115	-.128	.000	.057
Cleft lip	-.024	-.159	.052	.313	.447*	.000	.057
Cleft palate with cleft lip	.019	-.003	-.170	-.145	-.153	.000	.000
Renal agenesis	.108	.000	-.064	-.076	-.066	.000	.000
All anomalies	.204*	-.151	-.190	.157	.296	.189	-.149
n for anomalies ^c	85	33	41	25	25	6	6
Stillbirth	-.053	-.133	-.053	.032	.074	.309	-.235
Preterm birth	.021	.163	.035	.178	.148	.000	-.183
n for births ^c	141	35	41	42	42	10	4

^a For specific time periods, see Appendices I, II

^b 1 = fenitrothion formulations, 2 = aminocarb formulations, 3 = other insecticides, 4 = herbicides with any phenoxy component, 5 = phenoxy herbicides, 6 = chlorinated herbicides, 7 = non-chlorinated herbicides

^c Number of paired data points on which the correlation is based for anomalies, still and preterm births, respectively. This is determined by the number of county quarters sprayed. For degrees of freedom, subtract 2.

* nominally significant at $p < 0.05$

Table E5

Robustness of the overall linear association on n pairs of data (Tables 1-4) when highest spray value pairs are progressively removed.

Codes ^a			Correlation @ # data points				
Spray	Lag	Outcome	n ^b	n-1	n-2	n-3	n-4
1	2	1	.211	.170	.210	.191	.234
1	2	3	.306	.181	.215	.196	.232
1	3	8	.204	.222	.207	.241	.224
2	1	2	.384	.271	.175	.314	
* 2	2	5	.583	.391	.314	-.023	
3	2	7	.364	.517	.195	.236	.286
4	0	4	.350	.506	.302	.360	
* 4	2	4	.631	-.049	-.033		
4	3	5	.313	.522	.627		
* 4	0	6	.374	.043	.063	.085	
4	0	8	.378	.419	.346	.191	
4	2	8	.485	.410	.363		
(*)4	3	8	.157	.422	.480		
5	3	1	.297	.378	.463		
5	2	3	.387	.361	.456		
(*)5	3	3	.294	.389	.490		
5	0	4	.374	.444	.227	.283	
* 5	2	4	.443	-.036	-.017		
5	3	5	.447	.563	.685		
5	0	8	.409	.412	.343	.178	
5	2	8	.437	.351	.294		
(*)5	3	8	.296	.462	.533		
4	0	9	.539	.196	.070	.145	.248
5	0	9	.596	.235	.123	.218	.281

^a Spray codes correspond to columns, Tables 1-4; Outcomes correspond to rows, i.e. 4 = cleft palate, 9 = stillbirth, etc.

^b See Tables 1-4 for these values and the original numbers of data points.

* To illustrate this approach (table 5), originally "strong" associations whose effect seems due to a few outliers are marked with an asterisk. In addition, a few originally "weak" overall associations have been investigated because it appeared, from the scatter diagrams, that an outlier was depressing the value of the underlying association. These are marked by an asterisk in parenthesis.

TABLE E6

Insecticides and Stillbirth Temporal Analysis

(Direction of Differences observed by comparing Mean Rates of Occurrence when Insecticide Spraying took place, at lags 0, 1, 2 and 3 quarters, with Corresponding Mean Rates for Remaining Quarters of the Year)

County		Fenitrothion				Aminocarb				Other Insecticides			
		Lag				Lag				Lag			
		0	1	2	3	0	1	2	3	0	1	2	3
S O U T H	*01		+	+			+				+		
	02	+	+			+	+		+	+	+		
	*03			+	+		+		+		+	+	+
	*04			+		+	+				+	+	
	*05		+		+			+					
	06		+	+	+						+	+	+
	07		+		+	+	+	+					
	08	+	+			+	+			+	+		+
N O R T H	09		+	+			+	+		+	+	+	+
	*10	+	+		+					+	+		+
	*11	+		+					+	+	+		+
	*12		+			+					+	+	
	*13		+		+			+		+			
	14		+			+				+	+	+	
	15	+	+	+		+				+	+	+	+

* = Saint John River Basin

Note: Plus (+) signs represent positive directional differences -
- mean rates of occurrence when spraying took place (at lags 0,1,2 or 3 quarters) are higher than corresponding mean rates for remaining quarters of a year.

Blanks represent negative directional differences -
- mean rates lower than corresponding mean for remaining quarters of a year.

Table E7

-Summary-

Herbicides and Seven Congenital Anomalies Temporal Analysis

(Note: Each of the figures within a cell represents the number of anomalies for which the rate at any given lag interval is higher following spraying than the average rate for unsprayed lagged periods.)

County		Herbicide with Any Phenoxy Component				Phenoxy-herbicide				Chlorinated Herbicides				Non-Chlorinated Herbicides			
		0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
SOUTH THER	*01	4	3	3	1	4	4	3	1								
	02	0	0	0	0	0	0	0	0								
	*03	0	0	0	0	0	0	0	0	0	1	2	0				
	*04	0	0	0	0	0	0	0	0	1	1	2	0				
	*05	5	3	2	4	4	2	2	4								
	06	1	1	0	3	1	1	0	3								
	07	0	0	0	0	0	0	0	0								
	08	0	0	0	1	0	0	0	1								
NORTH RIVER THER	09	4	2	9	1	4	2	2	1								
	*10	2	1	4	3	2	2	4	3	1	0	0	0	2	2	3	0
	*11	1	4	4	1	1	4	4	1					0	2	2	1
	*12	5	2	1	5	5	2	1	5					5	1	0	1
	*13	2	2	4	4	2	2	4	4					2	2	3	4
	14	1	1	1	1	1	1	1	1								
	15	1	4	3	2	1	4	4	2								

* Saint John River Basin

TABLE E8

Correlation Analyses: Total Spina Bifida and Seven Pesticide Categories

EXPOSURE	TOTAL SPINA BIFIDA							
	LAG 0		LAG 1		LAG 2		LAG 3	
	r	n	r	n	r	n	r	n
Fenitrothion	-.011	85	.090	85	.190	85	-.121	97
Aminocarb	-.116	33	.143	33	-.186	33	.509*	19
Other Forest Insecticides	.020	41	.036	41	-.044	41	-.136	41
Any Phenoxy Herbicide	.052	32	-.046	32	.216	25	-.055	25
Phenoxy Herbicides	-.072	32	-.010	32	.306	25	-.072	25
Chlorinated Herbicides	.000	8	.000	8	.000	6	-.537	6
Non-chlorinated Herbicides	-.343	7	-.218	7	.942**	6	.000	6

* p < .05

** p < .01

TABLE E9

Total Spina Bifida and Seven Pesticide Categories
Comparison of Mean Rates Across Lag Intervals, All Counties

INSECTICIDES												HERBICIDES															
												ANY															
FENITROT.				AMINOCARB				OTHER				PHENOXY				PHENOXY				CHLORIN.				N-CHLORIN.			
0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
01			+		+						+	+	+	+	+	+	+	+									
02	+			+					+		+																
03																											
04																											
05			+								+																
06	+																										
07			+																								
08		+			+					+																	
09	+	+	+		+	+			+	+		+	+		+	+	+	+									
10	+	+			+	+						+		+	+		+				+	+					
11	+								+					+				+									
12		+	+			+			+					+			+								+		
13			+	+		+				+		+			+		+					+					
14	+		+			+	+																				
15					+							+			+												

Notes: Numbers in left hand column represent counties as listed in figure 8.
Plus (+) signs and blanks are explained in footnote of table E6.

TABLE E10

Correlation Analyses: Total Cleft Lip and Seven Pesticide Categories

EXPOSURE	TOTAL CLEFT LIP							
	LAG 0		LAG 1		LAG 2		LAG 3	
	r	n	r	n	r	n	r	n
Fenitrothion	-.129	85	.060	85	-.082	85	-.028	97
Aminocarb	-.157	33	-.182	33	-.018	33	.057	19
Other Forest Insecticides	.223	41	-.075	41	.338*	41	.360*	41
Any Phenoxy Herbicide	.155	32	NA	32	-.025	25	-.023	25
Phenoxy Herbicides	.226	32	NA	32	-.148	25	-.045	25
Chlorinated Herbicides	NA	8	NA	8	-.537	6	NA	6
Non-chlorinated Herbicides	NA	7	NA	7	NA	6	-.061	6

* $p < .05$

NA = Not available due to complete absence of cases

TABLE E11

Total Cleft Lip and Seven Pesticide Categories
Comparison of Mean Rates Across Lag Intervals, All Counties

INSECTICIDES												HERBICIDES															
												ANY															
FENITROT.				AMINOCARB				OTHER				PHENOXY				PHENOXY				CHLORIN.				N-CHLORIN.			
0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
01	+		+								+																
02			+						+		+	+															
03			+	+							+																
04	+																										
05			+	+																							
06			+	+																							
07				+																							
08	+		+							+																	
09	+		+	+	+		+					+															
10			+	+		+					+	+	+	+	+		+	+			+						
11	+																										
12											+																
13	+				+	+						+		+	+		+									+	
14	+	+		+		+		+	+																		
15				+							+																

Notes: Numbers in left hand column represent counties as listed in figure 8.
Plus (+) signs and blanks are explained in footnote of table E6.

TABLE E12

Significant ($p \leq .05$) Sign Test Results on Differences in Mean Outcome Rate Between Sprayed and Non-sprayed Time Periods By Outcome and Spray Category

LAG = 0 QUARTERS

OUTCOME	SPRAY CODE ^c						
	1	2	3	4	5	6	7
Anencephaly							
Spina bifida with hydrocephalus		.013					
Spina bifida without hydrocephalus				.000			
Cleft palate							
Cleft lip		.002	.039				
Cleft palate & cleft lip	.007 ^a	.002	.003				
Renal agenesis		.013	.022				
40 anomalies							
Premature birth							
Stillbirth							

^a All p-values denote a significantly higher number of negative differences where a difference is calculated as: mean rate in sprayed periods - mean rate in unsprayed periods. The numeric value is the p-value for a 2-tailed sign test.

^c 1 = fenitrothion formulations, 2 = aminocarb formulations, 3 = other insecticides, 4 = herbicides with any phenoxy component, 5 = phenoxy herbicides, 6 = chlorinated herbicides, 7 = non-chlorinated herbicides

TABLE E13

Significant ($p < .05$) Sign Test Results on Differences in Mean Outcome Rate Between Sprayed and Non-sprayed Time Periods By Outcome and Spray Category

LAG = 1 QUARTER

OUTCOME	SPRAY CODE ^c						
	1	2	3	4	5	6	7
Anencephaly							
Spina bifida with hydrocephalus			.013				
Spina bifida without hydrocephalus	.007 ^a	.013					
Cleft palate							
Cleft lip			.003				
Cleft palate & cleft lip	.035	.002					
Renal agenesis		.002	.022				
40 anomalies	.035 ^b		.013 ^b				
Premature birth							
Still birth	.035		.002				

^a All p-values not marked as "b" denote a significantly higher number of negative differences where a difference is calculated as: mean rate in sprayed periods - mean rate in unsprayed periods.

^b denotes a significantly higher number of positive differences. The numeric value is the p-value for a 2-tailed sign test.

^c 1 = fenitrothion formulations, 2 = aminocarb formulations, 3 = other insecticides, 4 = herbicides with any phenoxy component, 5 = phenoxy herbicides, 6 = chlorinated herbicides, 7 = non-chlorinated herbicides

TABLE E14

Significant ($p < .05$) Sign Test Results on Differences in Mean Outcome Rate Between Sprayed and Non-sprayed Time Periods By Outcome and Spray Category

LAG = 2 QUARTERS

OUTCOME	SPRAY CODE ^c						
	1	2	3	4	5	6	7
Anencephaly							
Spina bifida with hydrocephalus		.002 ^a		.039	.039		
Spina bifida without hydrocephalus							
Cleft palate							
Cleft lip			.022				
Cleft palate & cleft lip			.022				
Renal agenesis		.002	.022	.012			
40 anomalies							
Premature birth							
Still birth							

^a All p-values denote a significantly higher number of negative differences where a difference is calculated as: mean rate in sprayed periods - mean rate in unsprayed periods. The numeric value is the p-value for a 2-tailed sign test.

^c 1 = fenitrothion formulations, 2 = aminocarb formulations, 3 = other insecticides, 4 = herbicides with any phenoxy component, 5 = phenoxy herbicides, 6 = chlorinated herbicides, 7 = non-chlorinated herbicides

TABLE E15

Significant ($p \leq .05$) Sign Test Results on Differences in Mean Outcome Rate Between Sprayed and Non-sprayed Time Periods By Outcome and Spray Category

LAG = 4 QUARTERS

OUTCOME	SPRAY CODE ^c						
	1	2	3	4	5	6	7
Anencephaly				.022	.022		
Spina bifida with hydrocephalus							
Spina bifida without hydrocephalus							
Cleft palate			.021				
Cleft lip		.039 ^a					
Cleft palate & cleft lip							
Renal agenesis							
40 anomalies		.000 ^b					
Premature birth							
Still birth				.035	.035		

^a All p-values not marked as "b" denotes a significantly higher number of negative differences where a difference is calculated as: mean rate in sprayed periods - mean rate in unsprayed periods.

^b denotes a significantly higher number of positive differences. The numeric value is the p-value for a 2-tailed sign test.

^c 1 = fenitrothion formulations, 2 = aminocarb formulations, 3 = other insecticides, 4 = herbicides with any phenoxy component, 5 = phenoxy herbicides, 6 = chlorinated herbicides, 7 = non-chlorinated herbicides

TABLE F1

Paternal age distribution in stillbirths and controls by selected categories, frequency and percent

Paternal Age (yr)	Case/control status					
	stillbirths		control 1		control 2	
	f	%	f	%	f	%
19	12	4.0	7	2.3	12	3.9
20-24	68	22.8	79	26.4	74	24.4
25-29	70	23.5	103	34.4	104	34.4
30-34	45	15.1	56	18.7	50	16.5
35-39	25	8.4	25	8.4	20	6.6
40+	24	8.1	7	2.3	21	6.9
unknown	54	18.1	22	7.5	22	7.3
TOTALS	298	100.0	299	100.0	303	100.0

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F2.1

Maternal age distribution in stillbirths and controls by selected categories, frequency and percent

Maternal Age (yr)	Case/control status					
	stillbirths		control 1		control 2	
	f	%	f	%	f	%
19	57	19.1	36	12.0	51	16.8
20-24	97	32.6	126	42.2	117	38.7
25-29	86	28.9	89	29.9	81	26.8
30-34	32	10.7	39	13.0	33	10.9
35-39	17	5.7	7	2.3	15	4.8
40+	9	3.0	2	0.6	6	2.0
unknown	0		0		0	
TOTALS	298	100.0	299	100.0	303	100.0

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F2.2

Relation of stillbirth to maternal age, 1973-1980

Status	Maternal Age Group					
	19 ¹	20-24	25-29	30-34	35-39	40+
cases	57	97	86	32	17	9
controls	87	243	170	72	22	8
SRR	1.00	0.61	0.77	0.68	1.18	1.72
95% limits		0.40-0.94	0.49-1.21	0.38-1.20	0.54-2.56	0.57-5.25
χ^2		5.19	1.19	1.67	0.07	0.63
p		.0227	0.2758	0.1966	0.7890	0.4261

χ^2 , homogeneity = 11.170, 5df., p = 0.0481
 χ^2 , trend = 0.589, 1df., p=0.4427

¹ Referent category

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F3

Birth month distribution in stillbirths and controls,
frequency and percent

Birth Month	Case/control status					
	stillbirths		control 1		control 2	
	f	%	f	%	f	%
January	18	6.0	20	6.7	19	6.3
February	26	8.7	26	8.7	26	8.6
March	25	8.4	24	8.0	25	8.3
April	29	9.7	27	9.0	29	9.6
May	19	6.4	18	6.0	19	6.3
June	24	8.1	25	8.4	25	8.3
July	36	12.1	36	12.0	36	11.9
August	32	10.7	34	11.4	34	11.2
September	29	9.7	29	9.7	30	9.9
October	22	7.4	22	7.4	22	7.3
November	20	6.7	20	6.7	20	6.6
December	18	6.0	18	6.0	18	5.9
TOTALS	298	100.0	299	100.0	303	100.0

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F4

Year of birth distribution in stillbirths and controls,
frequency and percent

Year of Birth	Case/control status					
	stillbirths		control 1		control 2	
	f	%	f	%	f	%
1973	48	16.1	47	15.7	49	16.2
1974	49	16.4	49	16.4	49	16.2
1975	49	16.4	49	16.4	50	16.5
1976	42	14.1	43	14.4	43	14.2
1977	24	8.1	27	9.0	27	8.9
1978	28	9.4	27	9.0	27	8.9
1979	31	10.4	31	10.4	31	10.2
1980	27	19.1	26	18.7	27	8.9
TOTALS	298	100.0	299	100.0	303	100.0

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F5.1

Gestational age (weeks) distribution in stillbirths and controls,
frequency and percent

Gestation (weeks)	Case/control status					
	stillbirths		control 1		control 2	
	f	%	f	%	f	%
20-24	39	13.1	1	0.3	0	0.0
25-29	22	7.4	1	0.3	2	0.6
30-34	48	16.1	4	1.3	2	0.0
35	12	4.0	3	1.0	2	0.0
36	22	7.4	6	2.0	9	3.0
37	14	4.7	10	3.3	8	2.6
38	29	9.7	27	9.0	28	9.2
39	16	5.4	26	8.7	28	9.2
40	62	20.8	161	53.8	159	52.5
41	11	3.7	30	10.0	36	11.9
42	17	5.7	25	8.4	27	8.9
43+	6	2.0	5	1.6	6	2.0
TOTALS	298	100.0	299	100.0	303	100.0

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F5.2

Relation of stillbirth to gestational age, 1973-1980

Status	Gestational age categories				
	20-29	30-36	37-38	39-40	41+
cases	61	82	43	78	34
controls	4	22	73	374	129
SRR	1.00	0.24	0.04	0.01	0.02
95% limits		0.09-0.70	0.02-0.09	0.01-0.03	0.01-0.04
x ²		5.77	52.35	165.39	98.43
p		0.0163	0.0000	0.0000	0.0000

x², homogeneity = 269.3, 4df., p = 0.0000
x², trend¹ = 225.4, 1df., p=0.0000

¹ Category scores for trend = 0,1,2,3,4, respectively. Scoring categories as 50,10,5,0,2 produced a x², trend of 182.2, 1df., p=0.0000.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F6

Distribution of exposure opportunity scores for
stillbirth cases and controls

Chemical Group	Score	Case/control status		
		Stillbirth	Control 1	Control 2
Fenitrothion	-1 ¹	196	200	207
	0 ²	64	69	52
	1-10	17	11	18
	11-20	14	12	14
	21+	7	7	12
Aminocarb	-1	196	200	207
	0	99	95	96
	1-10	0	1	0
	11+	3	3	0
Phenoxy herbicides	-3 ³	59	61	80
	-1	177	179	177
	0	56	53	40
	1+	6	6	6
Agricultural herbicides	-1	123	124	124
	0	28	29	29
	1-5	8	8	5
	6-10	2	7	5
	11-20	10	29	13
	21-30	52	40	53
	31-40	20	17	25
	41+	55	45	51

1 -1 = not in exposure window

2 0 = within risk window but 0 exposure opportunity

3 -3 = no data available

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F7

Relationship of stillbirth to fenitrothion exposure opportunity, all controls

Status	Exposure category		
	0 ¹	1-10	11+
Cases	259	17	21
Controls ²	528	29	45
SRR	1.00	1.20	0.95
95% limits		0.62-2.30	0.54-1.68
x ²		0.16	0.60
p-value		0.6852	0.9642

x², homogeneity: 0.369, 2d.f., p=0.83148

x², trend = 0.002, 1d.f., p=0.9688

¹ combines those "not in first trimester exposure window" plus those "in window but unexposed".

² All controls.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F8

Relationship of stillbirth to fenitrothion exposure opportunity vs control 1

Status	Exposure category			
	NIW ¹	0 ²	1-10	11+
Cases	195	64	17	21
Controls ²	200	69	11	19
SRR	1.00	0.95	1.59	1.13
95% limits		0.63-1.44	0.68-3.72	0.56-2.28
x ²		0.02	0.93	0.04
p-value		0.8821	0.3352	0.8325

x², homogeneity: 1.628, 3d.f., p=0.6532

x², trend = 0.381, 1d.f., p=0.5368

¹ NIW = not in exposure window, referent group

² In spray window but no exposure

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F9

Relationship of stillbirth to fenitrothion exposure vs. control 2

Status	Exposure category			
	NIW ¹	0 ²	1-10	11+
Cases	195	64	17	21
Controls ²	207	52	18	26
SRR	1.00	1.31	1.00	0.86
95% limits		0.85-2.02	0.48-2.11	0.45-1.64
x ²		1.34	0.03	0.12
p-value		0.2468	0.8659	0.7322

x², homogeneity: 2.097, 3d.f., p=0.5526

x², trend = 0.015, 1d.f., p=0.9029

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F10

Standardized risk ratios for the relationship between stillbirth and exposure to agricultural chemical sprays by maternal county of residence

County	Exposure category scores		
	NIW ¹	0 ²	1+ ³
01	1.00	1.27	0.00
02		2.25	0.64
03		--	1.48
04		--	0.00
05		0.49	4.67
06		--	1.13
07		2.14	1.32
08		--	0.39
09		0.00	0.43
10		--	1.00
11		--	1.79
12		--	0.56
13		--	0.38
14		--	0.78
15		--	0.89
Summary	1.00	1.13	0.88

¹ Not in exposure window, referent.

² In window but zero exposure opportunity.

³ Any non-zero exposure opportunity.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F11

Standardized risk ratios for the relationship between stillbirth and exposure to agricultural chemical sprays by control group and within birth year category.

Birth year	Exposure Opportunity	Control Status		
		Control 1	Control 2	All Controls
1972-74	NIW	1.00	1.00	1.00
	0	1.65	0.90	1.12
	1-20	0.44	0.79	0.59
	21-30	2.10	0.86	1.15
	31-40	1.26	0.64	0.81
	41+	1.12	0.99	1.05
1975-77	NIW	1.00	1.00	1.00
	0	1.02	1.14	1.07
	1-20	0.45	1.12	0.61
	21-30	1.38	1.15	1.26
	31-40	1.11	1.06	1.09
	41+	1.55	1.29	1.42
1978-80	NIW	1.00	1.00	1.00
	0	0.51	1.37	0.70
	1-20	0.51	1.37	0.65
	21-30	0.84	1.28	1.00
	31-40	1.26	0.82	1.02
	41+	0.97	0.86	0.92

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F12.1

Relationship of stillbirth to agriculture
chemical spray

Status	Exposure opportunity category					
	0 ¹	1-10	11-20	21-30	31-40	41 ⁺
score ²	0	5	15	25	35	50
cases	151	10	10	52	20	55
controls ³	306	25	42	91	42	96
SRR	1.00	0.81	0.48	1.16	0.96	1.16
95% limits		0.35-1.82	0.22-10.3	0.77-1.75	0.53-1.76	0.78-1.74
x ²		0.13	3.40	0.40	0.00	0.44
p-value		0.7219	0.0615	0.5281	0.9834	0.5082

x², homogeneity:6.295, 5 d.f., p=0.2786

x², trend:0.731, 1 d.f., p=0.3926

¹ Includes "not in window" and "in window, zero exposure;" referent category

² Score for trend test

³ All controls

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F12.2

Relationship of stillbirth to agricultural
chemical spray

Status	Exposure category							
	NIW ¹	0	1-5	6-10	11-20	21-30	31-40	41 ⁺
cases	123	28	8	2	10	52	20	55
controls ²	124	29	8	7	29	40	17	45
SRR	1.00	0.97	1.01	0.29	0.35	1.31	1.19	1.23
95% limits		.53-1.80	.33-3.07	.06-1.30	.15-.78	.73-2.18	.56-2.51	.75-2.02
χ^2		0.00	.06	1.65	6.93	.96	.09	.58
p-value		.9561	.8089	.1993	.0085	.3281	.7595	.4482

χ^2 , homogeneity: 14.838, 7 d.f., $p=.0381$

χ^2 , trend: 0.698, 1 d.f., 0.4036

¹ "Not in window" referent category

² Control group 1.

Corresponding analysis vs. control 2 gives following SRR's: 1.00, 0.97, 1.61, 0.40, 0.78, 1.03, 0.81, 1.09, and χ^2 , het. = 3.061, 7 d.f., $p=0.8793$; χ^2 , trend: 0.000, 1 d.f., $p=.9962$. No SRR's significant.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F13.1

Relation of stillbirth to forest insecticide
window adjusted by north/south
maternal residence¹

Residence	Status	Forest insecticide window	
		No	Yes
south	cases	93	49
	controls ²	207	87
north	cases	100	56
	controls	199	109

Crude SRR³: 1.13, 95% limits³: 0.83-1.53

SRR, residence = south: 1.25, 95% limits⁴: 0.80-1.96

SRR, residence = north: 1.02, 95% limits⁴: 0.67-1.56

Summary OR: 1.12, 95% limits:⁵ 0.81-1.55, χ^2 for trend = 0.617,
p=0.4322

¹ South = counties 1-8, north = counties 9-15

² Total control sample

³ Referent category is window = no in all SRR calculations

⁴ Cornfield's limits

⁵ Test-based limits

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F13.2

Relation of stillbirth to forest
herbicide window, stratified by north/
south maternal residence¹

Maternal residence	Status	Forest herbicide window		Stratum-specific OR with 95% confidence limits
		No ²	Yes	
South	cases	86	56	OR=1.14, 95% limits: 0.74-1.75
	controls ³	187	107	
North	cases	92	64	0.88, 0.58-1.32
	controls	172	136	

Unadjusted analysis over 2 strata: OR=1.00, 95% limits = 0.74 - 1.34, χ^2 , trend = 0.010, 1 d.f., p=0.9203

Summary analysis over north/south residence: OR=0.99, 95% limits = 0.58-1.71, χ^2 , trend = 0.002, 1 d.f., p=0.9621

¹ South = counties 1-8, north = counties 9-15

² Referent group all calculations

³ Total control group

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F13.3

Relation of stillbirth to agriculture
window, stratified by north/
south maternal residence¹

Maternal residence	Status	Agriculture window		Stratum-specific OR with 95% confidence limits
		No	Yes	
South	cases	63	79	OR = 1.06, limits = 0.70-1.63
	controls ²	135	159	
North	cases	61	95	OR = 0.90 limits = 0.60-1.37
	controls	113	195	

Unadjusted analysis over 2 strata: OR=0.98, 95% limits = 0.73-1.32, χ^2 , trend:0.036, p=0.8487

Summary analysis adjusted for north/south residence: OR=0.98, 95% limits = 0.56-1.71, χ^2 , trend = 0.021, p=0.8838

¹ South = counties 1-8, north = counties 9-15

² Total control group

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F14

Relation of stillbirth to estimated date of
conception in agriculture, forest herbicide or
forest insecticide spray window stratified
by county and summarized over county,
1973-1980¹

County		Standardized Risk Ratios		
No.	Name	Agriculture window	Forest herbicide window	Forest insecticide window
01	Saint John	1.13	1.13	1.35
02	Charlotte	1.88	3.20	0.50
03	Sunbury	2.08	5.83	0.67
04	Queens	2.50	0.00	--2
05	Kings	0.78	0.47	2.05
06	Albert	1.50	6.00	1.00
07	Westmorland	1.50	1.33	1.80
08	Kent	0.44	0.17*	0.36
09	Northumberland	0.45	0.32*	0.74
10	York	1.68	1.89	0.80
11	Carleton	2.00	2.67	0.83
12	Victoria	0.67	0.29	2.75
13	Maddwaska	0.17	1.31	2.00
14	Restigouche	0.74	1.35	0.63
15	Gloucester	0.68	1.93	1.10
Summary OR		0.95	0.98	1.14
Test-based 95% confidence limits		0.59-1.53	0.32-3.02	0.77-1.70

* Significant at $p \leq 0.05$ (2-tailed)

¹ For control series 1 only

² SRR could not be calculated due to zero cell(s)

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F15.1

Relationship of stillbirth to forest
insecticide window, stratified by gestational
age group

Gestational age (weeks)	Status	Forest herbicide window		Stratum-specific OR ¹ with 95% confidence limits
		No ¹	Yes	
20-29	cases	39	22	OR: 1.69 limits: 0.17-17.18
	control ²	3	1	
30-36	cases	58	24	1.10 0.35-3.61
	controls	16	6	
37-38	cases	24	19	1.96 0.83-4.65
	controls	52	21	
39-40	cases	51	27	1.03 0.60-1.77
	controls	247	127	
41 ⁺	cases	21	13	1.33 0.56-3.11
	controls	88	41	

Unadjusted analysis over 5 strata: OR=1.13, 95% confidence limits =
0.83-1.53, χ^2 , trend = 0.526, p=0.4681

Summary analysis over gestational age: OR=1.25, 95% confidence limits =
0.86-1.83, χ^2 , trend = 1.615, p=0.2037

¹ Odds ratio (OR) calculations use window "NO" as the referent

² Total control group

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F15.2

Relationship of stillbirth to forest
herbicide window, stratified by maternal
age group

Maternal age (years)	Status	Forest herbicide window		Stratum-specific OR with 95% confidence limits
		No ¹	Yes	
19	cases	37	20	OR=0.73, 95% limits = 0.35-1.54
	control ²	50	37	
20-24	cases	61	36	0.87, 0.52-1.46
	controls	145	98	
25-29	cases	45	41	1.51, 0.86-2.64
	controls	151	105	
30-34	cases	16	16	1.18, 0.47-2.95
	controls	39	33	
35-39	cases	12	5	0.60, 0.13-2.79
	controls	13	9	
40+	cases	7	2	0.86, 0.09-8.64
	controls	6	2	

Unadjusted analysis over 6 categories: OR=1.00, 95% limits = 0.74-1.34,
 χ^2 , trend = 0.010, 1 d.f., p=0.9203

Summary analysis over maternal age: OR=1.01, 95% confidence limits =
0.27-3.80, χ^2 , trend = 0.009, 1 d.f., p=0.9262

¹ Referent category for all calculations

² Total control group

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F15.3

Relationship of stillbirth to agriculture window, stratified by gestational age categories

Gestational age (weeks)	Status	Agriculture window		Stratum-specific OR with 95% confidence limits
		No ¹	Yes	
20-29	cases	26	35	OR = 4.04 limits: 0.45-35.90
	control ²	3	1	
30-36	cases	40	42	1.05, 0.37-2.97
	controls	11	11	
37-38	cases	18	25	1.03, 0.45-2.36
	controls	31	42	
39-40	cases	26	52	1.28, 0.74-2.21
	controls	146	228	
41+	cases	14	20	1.13, 0.49-2.61
	controls	71	92	

Unadjusted analysis over 5 strata: OR=0.98, 95% confidence limits = 0.73-1.32, χ^2 , trend = 0.036, 1 d.f., p=0.8487

Summary analysis over gestational age: OR=1.20, 95% confidence limits = 0.83-1.74, χ^2 , trend = 1.092, 1 d.f., p=0.2961

¹ Window "NO" is the referent category in all calculations

² All control

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F16.1

Relationship of stillbirth to forest
insecticide window, stratified by maternal
age group

Maternal age (years)	Status	Forest herbicide window		Stratum-specific OR ² with 95% confidence limits
		No ¹	Yes	
19	cases	37	20	1.08, 0.50-2.32
	control ²	58	29	
20-24	cases	59	38	1.50, 0.89-2.52
	controls	170	73	
25-29	cases	61	25	0.83, 0.46-1.52
	controls	175	81	
30-34	cases	18	14	1.66, 0.65-4.26
	controls	49	23	
35-39	cases	11	6	0.38, 0.08-1.67
	controls	9	13	
40+	cases	7	2	0.86, 0.09-8.64
	controls	6	2	

Unadjusted analysis over 6 categories: OR=1.13, 95% limits = 0.83-1.53,
x², trend = 0.526, p=0.4681

Summary analysis adjusted by maternal age: OR=1.12, 95% confidence
limits = 0.81-1.55, x², trend = 0.557, p=0.4556

¹ Odds ratio (OR) calculations use window = "NO" as the referent

² Total control group

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F16.2

Relationship of stillbirth to forest
herbicide window, stratified by gestational
age group

Gestational age (years)	Status	Forest herbicide window		Stratum-specific OR with 95% confidence limits
		No ¹	Yes	
20-29	cases control ²	41 3	20 1	OR=1.46, 95% limits = 0.14-15.06
30-36	cases controls	52 12	30 10	0.69, 0.24-1.99
37-38	cases controls	28 49	15 24	1.09, 0.46-2.61
39-40	cases controls	40 214	38 160	1.27, 0.76-2.13
41+	cases controls	17 81	17 48	1.69, 0.74-3.86

Unadjusted analysis over 5 strata: OR=1.00, 95% confidence limits =
0.74-1.34, χ^2 , trend = 0.010, 1 d.f., p=0.9203

Summary analysis over gestational age: OR=1.21, 95% confidence limits =
0.84-1.75, χ^2 , trend = 1.289, 1 d.f., p=0.2562

¹ Referent category for all calculations

² Total control group

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F16.3

Relationship of stillbirth to agriculture
window, stratified by maternal age

Maternal age (years)	Status	Agriculture window		Stratum-specific OR with 95% confidence limits
		No ¹	Yes	
19	cases	26	31	OR = 0.88 limits = 0.43-1.83
	control ²	37	50	
20-24	cases	42	55	1.00, 0.60-1.65
	controls	105	138	
25-29	cases	32	54	1.13, 0.64-1.99
	controls	68	102	
30-34	cases	10	22	1.17, 0.44-3.14
	controls	25	47	
35-39	cases	8	9	0.78, 0.18-3.37
	controls	9	13	
40+	cases	6	3	0.50, 0.04-5.23
	controls	4	4	

Unadjusted analysis over 6 strata: OR=0.98, 95% limits = 0.73-1.32, χ^2 ,
trend = 0.036, p=0.8487

Summary analysis over maternal age: OR=1.00, 95% confidence limits =
0.96-1.04, χ^2 , trend = 0.000, 1 d.f., p=0.9934

¹ Referent group, all calculations

² All controls

NOTE: Abbreviations are explained in the Compendium of Abbreviations (page 123)

TABLE F17.1

Risk¹ of a congenital anomaly² after conception in the forest insecticide spray window, both control groups, by sex of case.

Analysis	Forest Insecticide Window	
	NO ³	YES
Crude	1.00	0.97
Sex = male		0.96
Sex = female		0.98
Adjusted for sex		0.97

¹ Risk is the risk ratio standardized to the "NO" category in each analysis

² All anomalies in the seven groups considered.

³ Referent

*Note that "risk" is based on SRR or derived from case control study, and does not imply prospective information.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F17.2

Risk¹ of a congenital anomaly² after conception in the forest herbicide spray window, both control groups, by sex of case.

Analysis	Forest Insecticide Window	
	NO ³	YES
Crude	1.00	1.12
Sex = male		1.21
Sex = female		1.04
Adjusted for sex		1.12

¹ Risk is the risk ratio standardized to the "NO" category in each analysis.

² All anomalies in the seven groups considered.

³ Referent

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F17.3

Risk¹ of a congenital anomaly² after conception in the agricultural spraying window, both control groups, by sex of case.

Analysis	Forest Insecticide Window	
	NO ³	YES
Crude	1.00	1.03
Sex = male		1.11
Sex = female		0.96
Adjusted for sex		1.03

¹ Risk is the risk ratio standardized to the "NO" category in each analysis.

² All anomalies in the seven groups considered.

³ Referent

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F17.4

Risk¹ of a congenital anomaly² after exposure to phenoxy herbicides in the conception window by control group

Analysis	Phenoxy herbicide exposure category			
	NIW ³	NE ⁴	Any ⁵	NDA ⁶
Control Group 1:				
SRR	1.00	1.02	0.50	0.93
Lower 95% limit		0.71	0.09	0.62
Upper 95% limit		1.45	2.69	1.40
Control Group 2:				
SRR	1.00	2.11	1.05	0.60*
Lower 95% limit		1.51	0.19	0.43
Upper 95% limit		2.97	5.76	0.84

* SRR significant at $p \leq 0.05$

¹ Risk is given as risk ratio standardized to NIW category in each analysis.

² All anomalies in the seven groups considered.

³ Not In (conception) Window = referent

⁴ Not Exposed (but in conception window)

⁵ Any phenoxy herbicide exposure opportunity

⁶ No Data Available (but in conception window)

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F18

Risk¹ of a congenital anomaly² after exposure to agricultural chemicals in the conception window by control group and SJRB residence³

Analysis	Agricultural chemical exposure categories							
	NIW ⁴	NE ⁵	1-5	6-10	11-20	21-30	31-40	41+
Control Group 1	1.00							
- Crude		0.91	2.17	1.01	1.09	0.75	0.87	1.16
- SJRB = NO		-- ⁶	1.70	0.81	0.65	1.08	0.72	0.97
- SJRB = YES		0.77	--	--	1.26	0.56	1.30	1.96
- Adjusted		0.90	2.33	1.08	1.03	0.75	0.90	1.23
Control Group 2	1.00							
- Crude		1.00	2.66	1.70	1.45	0.56	1.40	1.34
- SJRB = NO		4.28	2.35	1.28	1.60	0.53	1.25	1.30
- SJRB = YES		0.92	4.23	--	1.41	0.58	1.66	1.43
- Adjusted		1.03	2.69	1.73	1.45	0.56	1.41	1.35

¹ Risk ratio standardized to the NIW category in each analysis.

² All anomalies in the seven groups considered.

³ Maternal residence in St. John River Basin county or not.

⁴ Not In (conception) Window = referent.

⁵ Not Exposed (but in conception window).

⁶ SRR not calculated due to zero cell values.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 120)

TABLE F19.1

Risk of a congenital anomaly after exposure to fenitrothion in the conception window by control group and SJRB residence

Analysis	Fenitrothion exposure category			
	NIW	NE	1-10	11+
Control Group 1	1.00			
- Crude		0.74	1.94	1.26
- SJRB = NO		0.56	1.88	0.94
- SJRB = YES		0.99	2.04	1.74
- Adjusted for SJRB		0.74	2.01*	1.26
Control Group 2	1.00			
- Crude		1.05	0.94	0.97
- SJRB = NO		0.95	6.00	0.73
- SJRB = YES		1.16	0.80	1.35
- Adjusted for SJRB		1.05	0.99	0.97

*SRR significant at $p \leq 0.05$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F19.2

Risk of a congenital anomaly after exposure to fenitrothion in the conception window by control group and SJRB residence

Status	Fenitrotrion exposure category			
	NIW	NE	1-10	11+
SJRB = NO				
Cases	117	39	6	16
Controls	110	65	3	16
SRR	1.00	0.56	1.88	0.94
Lower 95% limit		0.34	0.47	0.42
Upper 95% limit		0.93	7.57	2.09
SJRB = YES				
Cases	112	44	25	18
Controls	119	47	13	11
SRR	1.00	0.99	2.04	1.74
Lower 95% limit		0.59	0.95	0.74
Upper 95% limit		1.66	4.46	4.14
Crude SRR	1.00	0.74	1.94	1.26
Lower 95% limit		0.52	0.99	0.71
Upper 95% limit		1.05	3.82	2.23
Adjusted SRR	1.00	0.74	2.01	1.26
Lower 95% limit		0.52	1.02	0.66
Upper 95% limit		1.06	3.97	2.38

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F20

Risk of a congenital anomaly after exposure to fenitrothion in the conception window by control group and north/south residence

Analysis	Fenitrotrion exposure category			
	NIW	NE	1-10	11+
<u>Control Group 1</u>	1.00			
- Crude		0.74	1.94	1.26
- South residence		0.89	2.14	1.10
- North residence		0.63	1.89	1.15
- Adjusted for residence		0.74	2.03*	1.14
<u>Control Group 2</u>	1.00			
- Crude		1.05	0.94	0.63
- South residence		1.00	1.45	0.27
- North residence		1.11	0.66	1.32
- Adjusted for residence		1.05	0.93	0.87

*SRR significant at $p \leq 0.05$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F21

Risk of a congenital anomaly after exposure to agricultural chemicals in the conception window by control group and north/south residence

Analysis	Agricultural chemical exposure categories							
	NIW	NE	1-5	6-10	11-20	21-30	31-40	41+
<u>Control Group 1</u>	1.00							
- Crude		0.91	2.17	1.01	1.09	0.75	0.87	1.16
- South residence		1.26	— ⁶	4.53	2.42	1.01	— ⁶	1.08
- North residence		— ⁶	1.05	0.52	0.70	0.55	0.46	2.49*
- Adjusted		1.37	1.84	0.90	0.96	0.62	0.77	1.46
<u>Control Group 2</u>	1.00							
- Crude		1.00	2.66	1.70	1.45	0.56	1.40	1.34
- South residence		0.98	5.49	— ⁶	1.76	0.37	— ⁶	1.07
- North residence		3.13	2.09	1.04	1.35	0.61	0.99	1.97*
- Adjusted		1.06	2.65	1.70	1.45	0.54	1.43	1.42

* SRR significant at $p \leq 0.05$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F22.1

Risk of a congenital anomaly after exposure to agricultural chemicals in the conception window by control group and year of conception grouping

Analysis	Agricultural Chemical Exposure Category				
	NIW	NE	1-10	11-30	31+
<u>Control Group 1</u>	1.00				
- Crude		0.85	1.45	0.80	0.99
- Conception Year:					
71-73		0.53	1.44	0.41	0.58
74-77		0.85	0.93	0.91	1.26
78-80		1.15	3.07	0.91	0.85
- Adjusted		0.81	1.43	0.79	0.96
<u>Control Group 2</u>	1.00				
- Crude		1.00	2.22*	0.75	1.36
- Conception Year:					
71-73		1.18	2.95	0.66	1.77
74-77		1.21	1.74	0.91	1.42
78-80		0.67	2.35	0.81	1.30
- Adjusted		1.08	2.14	0.82	1.49

* SRR significant at $p \leq 0.05$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F22.2

Risk¹ of a congenital anomaly² after exposure to agricultural chemicals in the conception window by control group and year of conception grouping

Analysis	Agricultural Chemical Exposure Category		
	NE	1-20	21+
<u>Control Group 1</u>	1.00		
- Crude		1.37	1.11
- Conception Quarter = 1		0.56	1.04
= 2		1.53	0.94
= 3		1.41	1.25
= 4		2.00	2.00
- Adjusted		1.32	1.11
<u>Control Group 2</u>	1.00		
- Crude		1.72	1.02
- Conception Quarter = 1		1.33	1.27
= 2		1.91	1.55
= 3		1.90	1.81
= 4		0.67	1.01
- Adjusted		1.76	1.01

¹ Risk is the risk ratio standardized to the NE category in each analysis.

² All anomalies in the seven groups considered.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F22.3

Risk¹ of a congenital anomaly² after exposure to fenitrothion
in the conception window by control group and quarter of conception

Analysis	Fenitrothion Exposure Category		
	NE	1-10	11+
<u>Control Group 1</u>	1.00		
- Crude		2.61*	1.70
- Conception Quarter = 1		5.24*	1.61
= 2		1.83	1.78
= 3		3.33	1.67
- Adjusted		2.60*	1.72
<u>Control Group 2</u>	1.00		
- Crude		0.89	0.92
- Conception Quarter = 1		1.44	1.09
= 2		0.66	0.95
= 3		2.00	0.33
- Adjusted		0.91	0.94

* SRR significant at $p \leq 0.05$

¹ Risk is the risk ratio standardized to the NE category in each analysis.

² All anomalies in the seven groups considered.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F22.4

Risk¹ of a congenital anomaly² after conception in the forest insecticide spray window by control group and gestational age category

Analysis	Forest Insecticide Spray Window	
	NO ³	YES
<u>Control Group 1</u>	1.00	
- Crude		0.94
- Gestational age (wk) 20-29		1.54
30-36		0.47
37-38		1.32
39-40		0.83
41+		1.28
- Adjusted for gestational age		0.90
<u>Control Group 2</u>	1.00	
- Crude		0.99
- Gestational age (wk) 20-29		--4
30-36		1.38
37-38		2.45
39-40		0.89
41+		0.63
- Adjusted for gestational age		1.01

¹ Standardized risk ratio with respect to window = NO category.

² All anomalies in the seven groups considered.

³ Referent.

⁴ SRR could not be calculated due to zero cells.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F22.5

Risk¹ of a congenital anomaly² after conception in the forest herbicide spray window by control group and gestational age category

Analysis	Forest Herbicide Spray Window	
	NO ³	YES
<u>Control Group 1</u>	1.00	
- Crude		1.01
- Gestational age (wk) 20-29		3.20
30-36		0.75
37-38		1.69
39-40		7.86
41+		1.14
- Adjusted for gestational age		0.99
<u>Control Group 2</u>	1.00	
- Crude		0.21
- Gestational age (wk) 20-29		— ⁴
30-36		2.26
37-38		1.46
39-40		1.07
41+		1.24
- Adjusted for gestational age		1.22

¹ Standardized risk ratio with respect to window = NO category.

² All anomalies in the seven groups considered.

³ Referent.

⁴ SRR could not be calculated due to zero cells.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F22.6

Risk¹ of a congenital anomaly² after conception in the agricultural spray window by control group and gestational age category

Analysis	Agricultural Window	
	NO ³	YES
<u>Control Group 1</u>	1.00	
- Crude		0.98
- Gestational age (wk) 20-29		5.00
30-36		0.46
37-38		2.07
39-40		0.83
41+		1.13
- Adjusted for gestational age		0.98
<u>Control Group 2</u>	1.00	
- Crude		1.06
- Gestational age (wk) 20-29		0.00
30-36		1.78
37-38		1.83
39-40		1.04
41+		0.71
- Adjusted for gestational age		1.10

¹ Standardized risk ratio with respect to window = NO category.

² All anomalies in the seven groups considered.

³ Referent.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F22.7

Risk¹ of a congenital anomaly² after conception in any spray window by control group and gestational age category

Analysis	Any Spray Window	
	NO ³	YES
<u>Control Group 1</u>	1.00	
- Crude		0.93
- Gestational age (wk) 20-29		5.00
30-36		0.23
37-38		2.09
39-40		0.78
41+		1.17
- Adjusted for gestational age		0.92
<u>Control Group 2</u>	1.00	
- Crude		1.01
- Gestational age (wk) 20-29		0.00
30-36		1.33
37-38		1.70
39-40		1.98
41+		0.81
- Adjusted for gestational age		1.04

¹ Standardized risk ratio with respect to window = NO category.

² All anomalies in the seven groups considered.

³ Referent.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F23.1a

Risk of anencephaly after exposure opportunity to fenitrothion in the first trimester window by control group

Status	Fenitrothion exposure			
	NIW	NE	1-10	11+
Control Group 1				
Cases	62	20	12	9
Controls	229	112	16	27
SRR	1.00	0.66	2.77*	1.23
Lower 95% limit		0.37	1.16	0.51
Upper 95% limit		1.18	6.59	2.92
Chi-square		1.82	5.49	0.09
P-value		0.1773	0.0192	0.7699
Control Group 2				
Cases	62	20	12	9
Controls	235	81	34	36
SRR	1.00	0.94	1.34	0.95
Lower 95% limit		0.51	0.61	0.40
Upper 95% limit		1.70	2.87	2.18
Chi-square		0.01	0.37	0.00
P-value		0.9300	0.5444	0.9504

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F23.1b

Risk of Anencephaly After Exposure to Fenitrothion
in the first trimester window by north/south
residential status¹, all controls

ANALYSIS	FENITROTHION EXPOSURE			
	NIW	NE	1-10	11+
Residence = SOUTH				
Cases	22	7	6	0
Controls	219	95	22	23
SRR	1.00	0.73	2.71	0.00
Lower 95% limit		0.27	0.88	--
Upper 95% limit		1.89	8.07	--
Residence = NORTH				
Cases	40	13	6	9
Controls	245	98	28	40
SRR	1.00	0.81	1.31	1.38
Lower 95% limit		0.39	0.46	0.57
Upper 95% limit		1.65	3.60	3.23
Summary				
M-H OR	1.00	0.78	1.79	0.98
Lower 95% limit		0.42	0.83	0.80
Upper 95% limit		1.46	3.84	1.21

M-H Extension Chi-square: .123, 1 df., p = .7255

¹ Southern counties are 1-8, northern counties are 9-15

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F23.2a

Risk of anencephaly after exposure to agricultural chemicals in the first trimester window vs. control group 1

Status	Agricultural chemicals category				
	NIW	NE	1-10	11-30	31+
Cases	37	5	7	22	32
Controls	143	49	15	85	92
SRR	1.00	0.39	1.80	1.00	1.34
Lower 95% limit		0.13	0.61	0.53	0.76
Upper 95% limit		1.13	5.17	1.88	2.39
Chi-square		2.86	0.87	0.02	0.87
P-value		0.0908	0.3512	0.8810	0.3507
Chi-square, homogeneity: 7.736, 4 df., p = 0.1017					
Chi-square, trend: 2.233, 1 df., p = 0.1351					

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F23.2b

Risk of anencephaly after exposure to agricultural chemicals in conception window vs. control group 2

Status	Agricultural Chemicals Category				
	NIW	NE	1-10	11-30	31+
Cases	17	9	1	4	10
Controls	143	49	15	85	92
SRR	1.00	0.43	2.58	0.87	1.71
Lower 95% limit		0.14	0.83	0.47	0.95
Upper 95% limit		1.24	7.84	1.63	3.06
Chi-square		2.24	2.50	0.09	3.16
P-Value		0.1348	0.1139	0.7626	0.0754
Chi-square, homogeneity: 13.24, 4 df., p = 0.0010.					
Chi-square, trend: 4.266, 1 df., p = 0.0389.					
(Categories scored 0, 1, 5, 20, 40, respectively for trend test.)					

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F23.3

Risk of fenitrothion exposure in the first trimester conception window in anencephaly cases by gestational age categories, total controls

Analysis	Fenitrothion exposure category			
	NIW	NE	1-10	11+
<u>Gestation = 20 -36 weeks</u>				
- Cases	29	18	5	3
- Controls	27	18	3	4
- SRR	1.00	0.99	1.55	0.70
- Chi-square		0.00	0.04	0.00
- P-value		.9632	.8510	.9647
<u>Gestation = 37+ weeks</u>				
- Cases	33	2	7	6
- Controls	437	175	47	59
- SRR	1.00	0.15*	1.97	1.35
- Chi-square		7.60	1.65	0.15
- p-value		.0058	.1986	.6985
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	0.45*	1.84	1.13
- Lower 95% limit		0.22	0.77	0.08
- Upper 95% limit		0.93	4.39	16.62

* SRR significant at p 0.05

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F23.4

Risk of fenitrothion exposure in the first trimester conception window (SRR values) in anencephaly cases by control group and maternal SJRB residential status

Analysis	Fenitrothion exposure category			
	NIW	NE	1-10	11+
<u>Control Group 1</u>				
- SJRB = NO	1.00	0.39	1.05	0.79
- SJRB = YES	1.00	1.13	3.73*	2.00
- Summary analysis	1.00	0.66	3.05*	1.21
<u>Control Group 2</u>				
- SJRB = NO	1.00	0.65	3.34	0.61
- SJRB = YES	1.00	1.31	1.46	1.56
- Summary analysis	1.00	0.94	1.54	0.94

* SRR significant at $p \leq 0.05$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F23.5

Risk of agricultural chemical exposure in the first trimester conception window in anencephalus cases by maternal north/south¹ residence, all controls

Analysis	Agricultural chemical exposure			
	NIW	NE	1-20	21+
<u>Southern Counties</u>				
- Cases	13	5	4	13
- Controls	133	95	12	119
- SRR	1.00	0.54	3.41	1.12
- Chi-square		0.82	2.43	0.00
- P-value		.3361	.1188	.9492
<u>Northern Counties</u>				
- Cases	24	0	11	33
- Controls	160	1	64	186
- SRR	1.00	0.00	1.15	1.18
- Chi-square		1.21	0.02	0.19
- p-value		.2705	.8840	.6621
<u>Summary Analysis</u>				
- Mantel-Haenszel or	1.00	0.52	1.46	1.16
- Lower 95% limit		0.14	0.68	0.66
- Upper 95% limit		1.97	3.14	2.05

¹ Southern counties are 1-8, northern counties are 9-15.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F23.6

Risk of exposure to agricultural chemicals in the first trimester
conception window in anencephaly cases by maternal SJRB¹
residential status, all controls

Analysis	Agricultural chemical exposure categories						
	NIW	NE	1-10	11-20	21-30	31-40	41+
<u>SJRB = No</u>							
- Cases	18	1	4	2	5	5	13
- Controls	155	1	25	14	60	33	87
- SRR	1.00	8.61	1.38	1.23	0.72	1.30	1.29
- Chi-square		0.42	0.05	0.03	0.15	0.04	0.20
- p-value		.5191	.8263	.8700	.7010	.8374	.6510
<u>SJRB = Yes</u>							
- Cases	19	4	3	6	9	3	11
- Controls	138	95	1	36	77	15	33
- SRR	1.00	0.31	21.79	1.21	0.85	1.45	2.42
- Chi-square		3.87	8.24	0.01	0.03	0.03	3.53
- p-value		.0490	.0041	.9069	.8637	.8591	.0604
<u>Summary Analysis</u>							
- Mantel-Haenzel OR	1.00	0.43	2.40	1.22	0.79	1.36	1.69
- Lower 95% limit		0.15	0.85	0.24	0.34	0.41	0.92
- Upper 95% limit		1.22	6.84	6.17	1.85	4.54	3.08

¹ Southern counties are 1-8, northern counties are 9-15.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F24.1

Risk of spina bifida after exposure to fenitrothion in the first trimester window by control group

Status	Fenitrothion exposure			
	NIW	NE	1-10	11+
Control Group 1				
Cases	82	30	10	10
Controls	229	112	16	27
SRR	1.00	0.75	1.75	1.03
Lower 95% limit		0.45	0.70	0.45
Upper 95% limit		1.23	4.28	2.35
Chi-square		1.17	1.21	0.01
P-value		0.2799	0.2717	0.9117
Control Group 2				
Controls	235	81	34	36
SRR	1.00	1.06	0.84	0.80
Lower 95% limit		0.63	0.37	0.35
Upper 95% limit		1.78	1.87	1.76
Chi-square		0.01	0.07	0.18
P-value		0.9096	0.7926	0.6748

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 120)

Table F24.2a

Risk of spina bifida, all types after exposure to agricultural chemicals in first trimester window vs. control group 1

Status	Agricultural chemicals categories				
	NIW	NE	1-10	11-30	31+
Cases	52	16	5	26	33
Controls	143	49	15	85	92
SRR	1.00	0.90	0.92	0.84	0.99
Lower 95% limit		0.45	0.28	0.47	0.57
Upper 95% limit		1.79	2.88	1.50	1.69
Chi-square		0.03	0.01	0.24	0.01
P-value		0.8708	0.9165	0.6251	0.9387

Chi-square, homogeneity: 0.471, 4 df., p = 0.9763

Chi-square, trend: 0.003, 1 df., p = 0.9575

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F24.2b

Risk of spina bifida, all types after exposure to agricultural chemicals in first trimester window vs. control group 2

Status	Agricultural chemicals categories				
	NIW	NE	1-10	11-30	31+
Cases	52	16	5	26	33
Controls	150	47	11	102	76
SRR	1.00	0.98	1.31	0.74	1.25
Lower 95% limit		0.49	0.38	0.42	0.72
Upper 95% limit		1.96	4.35	1.29	2.17
Chi-square		0.01	0.03	0.99	0.52
P-value		0.9123	0.8519	0.3188	0.4707

Chi-square, homogeneity: 3.401, 4 df., p = 0.4930

Chi-square, trend: 0.264, 1 df., p = 0.6077

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F25.1

Risk of spina bifida with hydrocephalus after exposure to fenitrothion in the first trimester window by control group

Status	Fenitrothion exposure			
	NIW	NE	1-10	11+
Control Group 1				
Cases	37	14	3	4
Controls	229	112	16	27
SRR	1.00	0.77	1.16	0.92
Lower 95% limit		0.38	1.32	0.26
Upper 95% limit		1.55	4.18	2.97
Chi-square		0.37	0.01	0.01
P-value		0.5434	0.9094	0.9036
Control Group 2				
Controls	235	81	34	36
SRR	1.00	1.10	0.56	0.71
Lower 95% limit		0.53	0.17	0.24
Upper 95% limit		2.23	1.89	2.09
Chi-square		0.01	0.45	0.14
P-value		0.9182	0.5015	0.7050

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F25.2a

Risk of spina bifida with hydrocephalus after exposure to agricultural chemicals in first trimester window vs. control group 1

Status	Agricultural chemicals categories				
	NIW	NE	1-10	11-30	31+
Cases	25	6	4	10	13
Controls	143	49	15	85	92
SRR	1.00	0.70	1.53	0.67	0.81
Lower 95% limit		0.24	0.39	0.29	0.37
Upper 95% limit		1.94	5.49	1.55	1.75
Chi-square		0.26	0.14	0.65	0.16
P-value		0.6077	0.7121	0.4190	0.6891

Chi-square, homogeneity: 2.347, 4 df., $p = 0.6722$

Chi-square, trend: 0.413, 1 df., $p = 0.5206$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F25.2b

Risk of spina bifida with hydrocephalus after exposure to agricultural chemicals in first trimester window vs. control group 2

Status	Agricultural chemicals categories				
	NIW	NE	1-10	11-30	31+
Cases	25	6	4	10	13
Controls	150	47	11	102	76
SRR	1.00	0.77	2.18	0.59	1.03
Lower 95% limit		0.26	0.54	0.25	0.47
Upper 95% limit		2.12	8.26	1.35	2.23
Chi-square		0.10	0.82	1.36	0.01
P-value		0.7472	0.3664	0.2436	0.9085

Chi-square, homogeneity: 4.678, 4 df., $p = 0.3219$

Chi-square, trend: 0.068, 1 df., $p = 0.7949$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.1

Risk of spina bifida without hydrocephalus after exposure to fenitrothion in the first trimester window by control group

Status	Fenitrothion exposure			
	NIW	NE	1-10	11+
Control Group 1				
Cases	45	16	7	6
Controls	229	112	16	27
SRR	1.00	0.73	2.23	1.13
Lower 95% limit		0.38	0.78	0.39
Upper 95% limit		1.39	6.19	3.09
Chi-square		0.76	1.99	0.00
P-value		0.3837	0.1584	0.9929
Control Group 2				
Controls	235	81	34	36
SRR	1.00	1.03	1.08	0.87
Lower 95% limit		0.53	0.41	0.31
Upper 95% limit		2.00	2.74	2.32
Chi-square		0.00	0.00	0.00
P-value		0.9503	0.9488	0.9451

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 120)

TABLE F26.2a

Risk of spina bifida without hydrocephalus after exposure to agricultural chemicals in first trimester window vs. control group 1

Status	Agricultural chemicals categories				
	NIW	NE	1-10	11-30	31+
Cases	27	10	1	16	20
Controls	143	49	15	85	92
SRR	1.00	1.08	0.35	1.00	1.15
Lower 95% limit		0.45	0.05	0.48	0.58
Upper 95% limit		2.54	2.57	2.05	2.27
Chi-square		0.00	0.44	0.03	0.07
P-value		0.9893	0.5076	0.8707	0.7859

Chi-square, homogeneity: 1.439, 4 df., p = 0.8373

Chi-square, trend: 0.227, 1 df., p = 0.6335

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.2b

Risk of spina bifida without hydrocephalus after exposure to agricultural chemicals in first trimester window vs. control group 2

Status	Agricultural chemicals categories				
	NIW	NE	1-10	11-30	31+
Cases	27	10	1	16	20
Controls	150	47	11	102	76
SRR	1.00	1.18	0.51	0.87	1.46
Lower 95% limit		0.49	0.06	0.42	0.73
Upper 95% limit		2.78	3.94	1.78	2.91
Chi-square		0.04	0.05	0.06	0.99
P-value		0.8392	0.8160	0.8139	0.3192

Chi-square, homogeneity: 2.869, 4 df., $p = 0.5799$

Chi-square, trend: 0.904, 1 df., $p = 0.3417$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.3a

Risk of fenitrothion exposure in the first trimester window in spina bifida with hydrocephalus cases by gestational age categories, total controls

Analysis	Fenitrothion exposure category			
	NIW	NE	1-10	11+
<u>Gestation = 20 -36 weeks</u>				
- Cases	5	2	0	0
- Controls	27	18	3	4
- SRR	1.00	0.60	0.00	0.00
- Chi-square		0.03	0.01	0.01
- P-value		.8736	.9033	.9331
<u>Gestation = 37+ weeks</u>				
- Cases	32	12	3	4
- Controls	437	175	47	59
- SRR	1.00	0.94	0.87	0.93
- Chi-square		0.00	0.01	0.02
- p-value		.9882	.9395	.8994
<u>Summary Analysis</u>				
- Mantel-Haenszel or	1.00	0.88	0.76	0.80
- Lower 95% limit		0.30	0.03	0.05
- Upper 95% limit		2.57	18.79	12.13

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.3b

Risk of fenitrothion exposure in the first trimester window in
spina bifida without hydrocephalus cases by gestational
age categories, total controls

Analysis	Fenitrothion exposure category			
	NIW	NE	1-10	11+
<u>Gestation = 20 -36 weeks</u>				
- Cases	12	3	1	3
- Controls	27	18	3	4
- SRR	1.00	0.38	0.75	1.69
- Chi-square		1.18	0.11	0.04
- P-value		.2780	.7426	.8507
<u>Gestation = 37+ weeks</u>				
- Cases	33	12	6	3
- Controls	437	175	47	59
- SRR	1.00	0.98	1.69	0.67
- Chi-square		0.01	0.73	0.14
- p-value		.9039	.3937	.7086
<u>Summary Analysis</u>				
- Mantel-Haenszel or	1.00	0.81	1.48	0.90
- Lower 95% limit		0.38	0.46	0.00
- Upper 95% limit		1.71	4.76	99.99

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.3c

Risk of fenitrothion exposure in the first trimester window in
all spina bifida cases by gestational age categories,
total controls

Analysis	Fenitrothion exposure category			
	NIW	NE	1-10	11+
<u>Gestation = 20 -36 weeks</u>				
- Cases	17	5	1	3
- Controls	27	18	3	4
- SRR	1.00	0.44	0.53	1.19
- Chi-square		1.25	0.00	0.04
- P-value		.2644	1.00	.8397
<u>Gestation = 37+ weeks</u>				
- Cases	65	25	9	7
- Controls	437	175	47	59
- SRR	1.00	0.96	1.29	0.80
- Chi-square		0.00	0.20	0.12
- p-value		.9719	.6559	.7334
<u>Summary Analysis</u>				
- Mantel-Haenszel or	1.00	0.85	1.16	0.86
- Lower 95% limit		0.50	0.30	0.23
- Upper 95% limit		1.44	4.46	3.28

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.4a

Risk¹ of fenitrothion exposure in the first trimester window in spina bifida cases with mention of hydrocephalus by control group and maternal SJRB residential status

Analysis	Fenitrothion exposure category			
	NIW	NE	1-10	11+
<u>Control Group 1</u>	1.00			
- SJRB = NO		0.85	4.58	1.29
- SJRB = YES		0.72	0.44	0.52
- Summary analysis		0.79	1.15	0.93
<u>Control Group 2</u>	1.00			
- SJRB = NO		1.43	14.63*	1.00
- SJRB = YES		0.84	0.17	0.40
- Summary analysis		1.10	0.58	0.72

* SRR significant at $p \leq 0.05$

¹ Risk is given as a risk ratio standardized to the NIW category in each analysis.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.4b

Risk¹ of fenitrothion exposure in the first trimester window in spina bifida cases without hydrocephalus by control group and maternal SJRB residential status

Analysis	Fenitrothion exposure category			
	NIW	NE	1-10	11+
<u>Control Group 1</u>	1.00			
- SJRB = NO		0.38	0.00	0.97
- SJRB = YES		1.21	2.79	0.94
- Summary analysis		0.74	2.20	1.12
<u>Control Group 2</u>	1.00			
- SJRB = NO		0.65	0.00	0.97
- SJRB = YES		1.41	1.09	0.73
- Summary analysis		1.03	1.05	0.87

* SRR significant at $p \leq 0.05$

¹ Risk is given as a risk ratio standardized to the NIW category in each analysis.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

Table F26.4c

Risk¹ of fenitrothion exposure in the first trimester window
in all spina bifida cases by maternal SJRB residential status,
all controls

Analysis	Fenitrothion exposure category			
	NIW	NE	1-10	11+
<u>SJRB = NO</u>				
- Cases	38	13	2	7
- Controls	227	106	4	38
- SRR	1.00	0.73	2.99	1.10
- Chi-square		0.56	0.51	0.00
- P-value		.4542	.4754	.9882
<u>SJRB = YES</u>				
- Cases	44	17	8	3
- Controls	281	281	54	28
- SRR	1.00	1.05	0.94	0.65
- Chi-square		0.00	0.00	0.17
- p-value		.9945	.9615	.6759
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	0.89	1.11	0.90
- Lower 95% limit		0.50	0.11	0.13
- Upper 95% limit		1.58	11.05	6.27

¹ Risk is given as a risk ratio standardized to the NIW category in each analysis.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.5a

Risk¹ of exposure to agricultural chemicals in the first trimester window in spina bifida with hydrocephalus cases by maternal SJRB residential status, all controls

Analysis	Agricultural Chemical Exposure Category				
	NIW	NE	1-10	11-20	21+
<u>SJRB = NO</u>					
- Cases	10	0	3	1	15
- Controls	155	1	25	14	180
- SRR	1.00	0.00	1.86	1.11	1.29
- Chi-square		3.42	0.25	0.22	0.16
- p-value		.0646	.6175	.6399	.6905
<u>SJRB = YES</u>					
- Cases	15	6	1	4	3
- Controls	138	95	1	36	125
- SRR	1.00	0.58	9.20	1.02	0.22
- Chi-square		0.74	0.47	0.07	5.27
- p-value		.3899	.4937	.7946	.0217
<u>Summary Analysis</u>					
- Mantel-Haenszel OR	1.00	0.57	2.37	1.04	0.68
- Lower 95% limit		0.17	0.50	0.68	0.32
- Upper 95% limit		1.97	11.33	1.58	1.42

¹ Risk is given as a risk ratio standardized to the NIW category in each analysis.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.5b

Risk¹ of exposure to agricultural chemicals in the first trimester window in spina bifida without hydrocephalus cases by maternal SJRB residential status, all controls

Analysis	Agricultural Chemical Exposure Category				
	NIW	NE	1-10	11-20	21+
<u>SJRB = NO</u>					
- Cases	14	1	3	4	9
- Controls	155	1	25	14	180
- SRR	1.00	11.07*	0.85	0.48	1.15
- Chi-square		0.66	0.01	1.09	0.01
- p-value		.4158	.9415	.2961	.9393
<u>SJRB = YES</u>					
- Cases	13	9	4	7	10
- Controls	138	95	1	36	125
- SRR	1.00	1.01	1.15	0.81	3.22*
- Chi-square		0.05	0.01	0.04	5.51
- p-value		.8305	.9358	.8416	.0189
<u>Summary Analysis</u>					
- Mantel-Haenszel OR	1.00	1.17	1.00	0.64	1.82
- Lower 95% limit		0.16	0.97	0.27	0.93
- Upper 95% limit		8.61	1.62	1.49	3.55

¹ Risk is given as a risk ratio standardized to the NIW category in each analysis.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.5c

Risk¹ of agricultural chemical exposure in the first trimester window in all spina bifida cases by maternal SJRB residence, all controls

Analysis	Agricultural Chemical Exposure				
	NIW	NE	1-10	11-20	21+
<u>SJRB = NO</u>					
- Cases	24	1	6	5	24
- Controls	155	1	25	14	180
- SRR	1.00	6.46	1.55	2.31	0.86
- Chi-square		0.21	0.35	1.37	0.11
- p-value		.6456	.5524	.2425	.7418
<u>SJRB = YES</u>					
- Cases	28	15	5	11	13
- Controls	138	95	1	36	125
- SRR	1.00	0.78	24.64*	1.51	0.51
- Chi-square		0.31	12.42	0.65	2.96
- p-value		.5795	.0004	.4194	.0852
<u>Summary Analysis</u>					
- Mantel-Haenszel OR	1.00	0.86	2.79*	1.72	0.69
- Lower 95% limit		0.31	1.21	0.84	0.42
- Upper 95% limit		2.33	6.44	3.51	1.12

* SRR significant at p 0.05

¹ Risk is given as a risk ratio standardized to the NIW category in each analysis.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.6a

Risk of agricultural chemical exposure in the first trimester window in all spina bifida with hydrocephalus cases by maternal north/south¹ residence, all controls

Analysis	Agricultural Chemical Exposure			
	NIW	NE	1-20	21+
<u>SOUTH</u>				
- Cases	10	6	4	5
- Controls	133	95	12	119
- SRR	1.00	0.84	4.43*	0.56
- Chi-square		0.00	3.76	0.61
- p-value		.9486	.0525	.4354
<u>NORTH</u>				
- Cases	15	0	5	13
- Controls	160	1	64	186
- SRR	1.00	0.00	0.83	0.75
- Chi-square		2.21	0.01	0.30
- p-value		.1374	.9358	.5824
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	0.82	1.41	0.68
- Lower 95% limit		0.02	0.50	0.33
- Upper 95% limit		28.88	4.02	1.39

* SRR significant at $p \leq 0.05$

¹ Southern counties are 1-8, northern counties are 9-15

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.6b

Risk of agricultural chemical exposure in the first trimester window in all spina bifida without hydrocephalus cases by maternal north/south¹ residence, all controls

Analysis	Agricultural Chemical Exposure			
	NIW	NE	1-20	21+
<u>SOUTH</u>				
- Cases	8	8	1	8
- Controls	133	95	12	119
- SRR	1.00	1.40	1.39	1.12
- Chi-square		0.15	0.10	0.00
- p-value		.6967	.7490	.9663
<u>NORTH</u>				
- Cases	19	2	6	22
- Controls	160	1	64	186
- SRR	1.00	16.84*	0.79	1.00
- Chi-square		4.40	0.06	0.02
- p-value		.0360	.8047	.8780
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	1.90	0.86	1.03
- Lower 95% limit		0.67	0.08	0.18
- Upper 95% limit		5.40	9.47	6.02

¹ Southern counties are 1-8, northern counties are 9-15

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F26.6c

Risk of agricultural chemical exposure in the first trimester conception window in all spina bifida cases by maternal north/south¹ residence, all controls

Analysis	Agricultural Chemical Exposure			
	NIW	NE	1-20	21+
<u>SOUTH</u>				
- Cases	18	14	5	13
- Controls	133	95	12	119
- SRR	1.00	1.09	3.08	0.81
- Chi-square		0.00	2.60	0.13
- p-value		.9742	.1069	.7148
<u>NORTH</u>				
- Cases	34	2	11	35
- Controls	160	1	64	186
- SRR	1.00	9.41	0.81	0.89
- Chi-square		2.04	0.14	0.11
- p-value		.1529	.7036	.7425
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	1.30	1.12	0.86
- Lower 95% limit		0.52	0.38	0.52
- Upper 95% limit		3.23	3.32	1.43

¹ Southern counties are 1-8, northern counties are 9-15

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.1

Risk of total cleft lip¹ after exposure to fenitrothion
in the first trimester window by control group

Status	Fenitrothion exposure			
	NIW	NE	1-10	11+
Control Group 1				
Cases	48	21	4	7
Controls	229	112	16	27
SRR	1.00	0.89	1.19	1.24
Lower 95% limit		0.49	0.32	0.46
Upper 95% limit		1.62	4.04	3.20
Chi-square		0.06	0.00	0.05
P-value		0.8036	0.9992	0.8168
Control Group 2				
Controls	235	81	34	36
SRR	1.00	1.27	0.58	0.95
Lower 95% limit		0.69	0.20	0.36
Upper 95% limit		2.33	1.68	2.40
Chi-square		0.45	0.60	0.01
P-value		0.5045	0.4382	0.9147

¹ Cleft lip plus cleft palate with cleft lip

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.2

Risk of cleft lip or cleft palate and lip after exposure to
agricultural chemicals in first trimester window vs. control group 1

Status	Agricultural chemicals categories				
	NIW	NE	1-10	11-30	31+
Cases	31	14	5	13	17
Controls	143	49	15	85	92
SRR	1.00	1.32	1.54	0.71	0.85
Lower 95% limit		0.61	0.45	0.33	0.42
Upper 95% limit		2.83	4.99	1.49	1.70
Chi-square		0.33	0.23	0.65	0.10
P-value		0.5650	0.6328	0.4205	0.7483

Global chi-square for homogeneity: 3.265, 4 df., p = 0.5145

Chi-square test for trend: 1.097, 1 df., p = 0.2948

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

Table F27.3

Risk of cleft lip or cleft palate and lip after exposure to agricultural chemicals in first trimester window vs. control group 2

Status	Agricultural chemicals categories				
	NIW	NE	1-10	11-30	31+
Cases	31	14	5	13	17
Controls	150	47	11	102	76
SRR	1.00	1.44	2.20	0.62	1.08
Lower 95% limit		0.67	0.61	0.29	0.54
Upper 95% limit		3.10	7.53	1.30	2.18
Chi-square		0.67	1.13	1.45	0.00
P-value		0.4127	0.2887	0.2290	0.9444

Global chi-square, homogeneity: 6.513, 4 df., p = 0.1640

Chi-square test for trend: 0.387, 1 df., p = 0.5341

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.4

Risk of cleft lip with cleft palate after exposure to fenitrothion in the conception window by control group

Status	Fenitrothion exposure		
	NIW	NE	Any
Control Group 1			
Cases	23	12	6
Controls	229	112	43
SRR	1.00	1.07	1.39
Lower 95% limit		0.48	0.47
Upper 95% limit		2.34	3.88
Chi-square		0.00	0.17
p-value		0.9872	0.6807
Control Group 2			
Cases	23	12	6
Controls	235	81	70
SRR	1.00	1.51	0.88
Lower 95% limit		0.67	0.31
Upper 95% limit		3.36	2.38
Chi-square		0.81	0.00
p-value		0.3695	0.9635

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.5

Risk of cleft lip with cleft palate after exposure to fenitrothion
in the first trimester window by control group

Status	Fenitrothion exposure			
	NIW	NE	1-10	11+
Control Group 1				
Cases	23	12	3	3
Controls	229	112	16	27
SRR	1.00	1.07	1.87	1.11
Lower 95% limit		0.48	0.51	1.31
Upper 95% limit		2.34	6.78	3.94
Chi-square		0.00	0.30	0.03
P-value		0.9872	0.5851	0.8593
Control Group 2				
Controls	235	81	34	36
SRR	1.00	1.51	0.90	0.85
Lower 95% limit		0.67	0.26	0.24
Upper 95% limit		3.36	3.17	2.98
Chi-square		0.81	0.02	0.00
P-value		0.3695	0.8824	0.9584

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.6

Risk of cleft lip with cleft palate after exposure to agricultural chemicals in first trimester window by control group

Status	Agricultural Chemical Exposure				
	NIW	NE	1-10	11-30	31+
Control Group 1					
Cases	17	9	1	4	10
Controls	143	49	15	85	92
SRR	1.00	1.55	0.56	0.40	0.91
Lower 95% limit		0.59	0.07	0.11	0.37
Upper 95% limit		3.97	4.42	1.31	2.22
Chi-square		0.56	0.01	2.04	0.00
P-Value		0.4553	0.9063	0.1534	0.9962
Control Group 2					
Cases	17	9	1	4	10
Controls	150	47	11	102	76
SRR	1.00	1.69	0.80	0.35	1.16
Lower 95% limit		0.65	0.10	0.10	0.47
Upper 95% limit		4.35	6.61	1.14	2.84
Chi-square		0.90	0.08	2.89	0.02
P-Value		0.3441	0.7713	0.0892	0.8901

Chi-square, homogeneity, control 1: 5.381, 4df., p = 0.2503

Chi-square, trend, control 1: 0.724, 1 df., p = 0.3949

Chi-square, homogeneity, control 2: 7.325, 4 df., p = 0.1192

Chi-square, trend, control 2: 0.291, 1 df., p = 0.5898

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.7

Risk of cleft lip after exposure to fenitrothion in the first trimester conception window by control group

Status	NIW	Fenitrothion exposure		
		NE	1-10	11+
Control Group 1				
Cases	25	9	1	4
Controls	229	112	16	27
SRR	1.00	0.74	0.57	1.36
Lower 95% limit		0.31	0.07	0.37
Upper 95% limit		1.72	4.40	4.54
Chi-square		0.32	0.01	0.05
P-value		0.5721	0.9114	0.8281
Control Group 2				
Cases	25	9	1	4
Controls	235	81	34	36
SRR	1.00	1.04	0.28	1.04
Lower 95% limit		0.43	0.04	0.29
Upper 95% limit		2.47	1.86	3.42
Chi-square		0.01	1.01	0.04
P-value		0.9202	0.3150	0.8334

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.3

Risk of cleft lip after exposure to agricultural chemicals
in first trimester window by control group

Status	Agricultural Chemical Exposure				
	NIW	NE	1-10	11-30	31+
Control Group 1					
Cases	14	5	4	9	7
Controls	143	49	15	85	92
SRR	1.00	1.04	2.72	1.08	0.78
Lower 95% limit		0.31	0.66	0.41	0.27
Upper 95% limit		3.32	10.52	2.81	2.16
Chi-square		0.04	1.55	0.00	0.08
P-Value		0.8420	0.2133	0.9591	0.7719
Control Group 2					
Cases	14	5	4	9	7
Controls	150	47	11	102	76
SRR	1.00	1.14	3.90	0.95	0.99
Lower 95% limit		0.34	0.90	0.36	0.34
Upper 95% limit		3.63	15.85	2.44	2.75
Chi-square		0.00	3.17	0.01	0.05
P-Value		0.9669	0.0749	0.9236	0.8308

Chi-square, homogeneity, control 1: 3.747, 4df., $p = 0.4413$

Chi-square, trend, control 1: 0.489, 1 df., $p = 0.4846$

Chi-square, homogeneity, control 2: 5.792, 4 df., $p = 0.2153$

Chi-square, trend, control 2: 0.148, 1 df., $p = 0.7004$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.9

Risk of cleft lip after exposure to fenitrothion in the first trimester window vs. control group 1

Status	Fenitrothion exposure categories			
	NIW	NE	1-10	11+
Cases	29	12	0	6
Controls	229	112	16	27
SRR	1.00	0.85	0.00	1.75
Lower 95% limit		0.39	-	0.59
Upper 95% limit		1.80	-	4.96
Chi-square		0.08	1.00	0.75
P-value		0.7755	0.3185	0.3851

Global chi-square, homogeneity: 3.970, 3 df., p = 0.2647

Chi-square, trend: 1.190, 1 df., p = 0.2753

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.10

Risk of cleft palate after exposure to agricultural chemicals in first trimester window vs. control group 1

Status	Agricultural chemicals exposure				
	NIW	NE	1-10	11-30	31+
Cases	20	4	5	6	12
Controls	143	49	15	85	92
SRR	1.00	0.58	2.38	0.50	0.93
Lower 95% limit		0.16	0.67	0.17	0.41
Upper 95% limit		1.93	8.07	1.40	2.12
Chi-square		0.49	1.48	1.47	0.00
P-value		0.4857	0.2239	0.2252	0.9891

Global chi-square, homogeneity: 6.786, 4 df., p = 0.1477

Chi-square, trend: 0.144, 1 df., p = 0.7047

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.11

Risk of cleft palate after exposure to agricultural chemicals
in first trimester window vs. control group 2

Status	Agricultural chemicals exposure				
	NIW	NE	1-10	11-30	31+
Cases	20	4	5	6	12
Controls	150	47	11	102	76
SRR	1.00	0.64	3.41	0.44	1.18
Lower 95% limit		0.18	0.92	0.15	0.51
Upper 95% limit		2.11	12.18	1.21	2.71
Chi-square		0.28	3.23	2.31	0.05
P-value		0.5950	0.0724	0.1288	0.8160

Chi-square, homogeneity: 11.313, 4 df., p = 0.0233

Chi-square, trend: 0.000, 1 df., p = 0.9823

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.12

Risk of fenitrothion exposure in the first trimester window
in cleft palate cases by gestational age categories,
total controls

Analysis	Fenitrothion exposure		
	NIW	NE	Any
<u>GESTATION = 20-36 weeks</u>			
- Cases	1	1	1
- Controls	27	18	7
- SRR	1.00	1.50	3.86
- Chi-square		0.20	0.01
- p-value		.6531	.9236
<u>GESTATION = 37+ weeks</u>			
- Cases	28	11	5
- Controls	437	175	106
- SRR	1.00	0.98	0.74
- Chi-square		0.02	0.15
- p-value		.8962	.6963
<u>Summary Analysis</u>			
- Mantel-Haenszel OR	1.00	1.01	0.85
- Lower 95% limit		0.93	0.08
- Upper 95% limit		1.08	9.30

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.13

Risk of fenitrothion exposure in the first trimester window
in cleft lip cases by gestational age categories,
total controls

Analysis	Fenitrothion exposure		
	NIW	NE	Any
<u>GESTATION = 20-36 weeks</u>			
- Cases	1	2	0
- Controls	27	18	7
- SRR	1.00	3.00	0.00
- Chi-square		0.09	0.56
- p-value		.7468	.4533
<u>GESTATION = 37+ weeks</u>			
- Cases	23	7	5
- Controls	437	175	106
- SRR	1.00	0.76	0.90
- Chi-square		0.17	0.00
- p-value		.6770	.9778
<u>Summary Analysis</u>			
- Mantel-Haenszel OR	1.00	0.89	0.86
- Lower 95% limit		0.08	0.01
- Upper 95% limit		9.47	71.94

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.14

Risk of fenitrothion exposure in the first trimester window
in cleft palate cases by maternal SJRB residential status,
all controls

Analysis	Fenitrothion exposure		
	NIW	NE	Any
<u>SJRB = NO</u>			
- Cases	16	8	0
- Controls	227	106	42
- SRR	1.00	1.07	0.00
- Chi-square		0.01	1.81
- p-value		0.9409	0.1782
<u>SJRB = YES</u>			
- Cases	13	4	6
- Controls	237	87	71
- SRR	1.00	0.84	1.54
- Chi-square		0.00	0.33
- p-value		0.9836	0.5682
<u>Summary Analysis*</u>			
- Mantel-Haenszel OR	1.00	0.98	0.84
- Lower 95% limit		0.61	0.08
- Upper 95% limit		1.56	8.74

* Summary odds ratio weighted by SJRB residential status

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.15

Risk of fenitrothion exposure in the first trimester conception window in cleft lip cases by maternal SJRB residential status, all controls

Analysis	Fenitrothion exposure		
	NIW	NE	Any
<u>SJRB = NO</u>			
- Cases	12	7	1
- Controls	227	106	42
- SRR	1.00	1.25	0.45
- Chi-square		0.04	1.14
- p-value		0.8398	0.7037
<u>SJRB = YES</u>			
- Cases	13	2	4
- Controls	237	87	71
- SRR	1.00	0.42	1.03
- Chi-square		0.74	0.06
- p-value		0.3888	0.8027
<u>Summary Analysis</u>			
- Mantel-Haenszel OR	1.00	0.85	0.80
- Lower 95% limit		0.18	0.09
- Upper 95% limit		3.92	7.46

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.16

Risk of exposure to agricultural chemicals in the first trimester window in cleft palate cases by maternal SJRB residential status, all controls

Analysis	Agricultural chemical exposure			
	NIW	NE	1-20	21+
<u>SJRB = NO</u>				
- Cases	13	0	4	7
- Controls	155	1	39	180
- SRR	1.00	0.00	1.22	0.46
- Chi-square		2.52	0.00	1.95
- p-value		.1124	.9822	.1623
<u>SJRB = YES</u>				
- Cases	7	4	4	8
- Controls	138	95	37	125
- SRR	1.00	0.83	2.13	1.26
- Chi-square		0.00	0.65	0.03
- p-value		.9815	.4213	.8636
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	0.81	1.56	0.72
- Lower 95% limit		0.00	0.51	0.31
- Upper 95% limit		99.99	4.77	1.66

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.17

Risk of agricultural chemical exposure in the first trimester window in cleft palate cases by maternal north/south¹ residence, all controls

Analysis	Agricultural chemical exposure			
	NIW	NE	1-20	21+
<u>SOUTH</u>				
- Cases	4	4	2	8
- Controls	133	95	12	119
- SRR	1.00	1.40	5.54	2.24
- Chi-square		0.01	1.83	1.04
- p-value		.9165	.1767	.3080
<u>NORTH</u>				
- Cases	16	0	6	7
- Controls	160	1	64	186
- SRR	1.00	0.00	0.94	0.38*
- Chi-square		2.04	0.01	3.80
- p-value		.1532	.9057	.0511
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	1.33	1.26	0.72
- Lower 95% limit		0.00	0.30	0.32
- Upper 95% limit		99.99	5.33	1.62

¹ Southern counties are 1-8, northern counties are 9-15.

* $p \leq .05$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.18

Risk of agricultural chemical exposure in the first trimester window in cleft lip cases by maternal north/south¹ residence, all controls

Analysis	Agricultural chemical exposure			
	NIW	NE	1-20	21+
<u>SOUTH</u>				
- Cases	6	5	1	6
- Controls	133	95	12	119
- SRR	1.00	1.17	1.85	1.12
- Chi-square		0.00	0.02	0.01
- p-value		.9490	.8917	.9145
<u>NORTH</u>				
- Cases	8	0	6	7
- Controls	160	1	64	186
- SRR	1.00	0.00*	1.88	0.75
- Chi-square		4.54	0.70	0.08
- p-value		.0330	.4043	.7839
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	1.14	1.87	0.90
- Lower 95% limit		0.07	0.54	0.06
- Upper 95% limit		19.61	6.49	13.11

¹ Southern counties are 1-8, northern counties are 9-15.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.19

Risk of agricultural chemical exposure in the first trimester window in cleft lip with cleft palate cases by maternal north/south¹ residence, all controls

Analysis	Agricultural chemical exposure			
	NIW	NE	1-20	21+
<u>SOUTH</u>				
- Cases	9	8	3	5
- Controls	133	95	12	119
- SRR	1.00	1.24	3.69	0.62
- Chi-square		0.03	1.90	0.32
- p-value		.8576	.1680	.5729
<u>NORTH</u>				
- Cases	8	1	0	7
- Controls	160	1	64	186
- SRR	1.00	20.00	0.00	0.75
- Chi-square		1.56	1.88	0.08
- p-value		.2119	.1703	.7839
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	1.49	0.88	0.69
- Lower 95% limit		0.42	0.06	0.27
- Upper 95% limit		1.49	13.87	1.76

¹ Southern counties are 1-8, northern counties are 9-15.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F27.20

Risk of agricultural chemical exposure in the first trimester window in all cleft lip cases by maternal north/south¹ residence, all controls

Analysis	Agricultural chemical exposure			
	NIW	NE	1-20	21+
<u>SOUTH</u>				
- Cases	15	13	4	11
- Controls	133	95	12	119
- SRR	1.00	1.21	2.96	0.82
- Chi-square		0.08	1.82	0.07
- p-value		.7808	.1771	.7862
<u>NORTH</u>				
- Cases	16	1	6	14
- Controls	160	1	64	186
- SRR	1.00	10.00	0.94	0.75
- Chi-square		0.56	0.01	0.31
- p-value		.4560	.9057	.5788
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	1.35	1.36	0.78
- Lower 95% limit		0.50	0.49	0.41
- Upper 95% limit		3.65	3.78	1.51

¹ Southern counties are 1-8, northern counties are 9-15.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F28.1

Risk of renal agenesis after exposure to fenitrothion in the first trimester window by control group

Status	Fenitrothion exposure			
	NIW	NE	1-10	11+
Control Group 1				
Cases	17	5	6	2
Controls	229	112	16	27
SRR	1.00	0.60	5.05	1.00
Lower 95% limit		0.19	1.53	0.22
Upper 95% limit		1.79	16.19	4.57
Chi-square		0.56	8.20	0.15
P-value		0.4546	0.0042	0.7013
Control Group 2				
Cases	17	5	6	2
Controls	235	81	34	36
SRR	1.00	0.85	2.44	0.77
Lower 95% limit		0.27	0.80	0.17
Upper 95% limit		2.56	7.19	3.46
Chi-square		0.00	2.20	0.00
P-value		0.9606	0.1384	0.9942

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

Table F28.2a

Risk of renal agenesis after exposure to agricultural chemicals in first trimester window vs. control group 1

Status	Agricultural chemical group				
	NIW	NE	1-10	11-30	31+
Cases	7	5	2	7	9
Controls	143	49	15	85	92
SRR	1.00	2.08	2.72	1.68	2.00
Lower 95% limit		0.54	0.55	0.51	0.65
Upper 95% limit		7.77	13.54	5.56	6.20
Chi-square		0.79	0.44	0.44	1.18
P-value		0.3732	0.5095	0.5050	0.2783

Global chi-square, homogeneity: 2.755, 4 df., $p = 0.5997$

Chi-square, trend: 0.818, 1 df., $p = 0.3658$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F28.2b

Risk of renal agenesis after exposure to agricultural chemicals
in first trimester window vs. control group 2

Status	Agricultural chemical group				
	NIW	NE	1-10	11-30	31+
Cases	7	5	2	7	9
Controls	150	47	11	102	76
SRR	1.00	2.28	3.90	1.47	2.54
Lower 95% limit		0.59	0.80	0.45	0.83
Upper 95% limit		8.51	18.94	4.84	7.92
Chi-square		1.08	1.09	0.18	2.43
P-value		0.2988	0.2969	0.6706	0.1193

Global chi-square, homogeneity: 5.063, 4 df., p = 0.2809

Chi-square, trend: 1.571, 1 df., p = 0.2100

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F28.3

Risk of fenitrothion exposure in the first trimester window in
renal agenesis cases by gestational age categories, total controls

Analysis	Fenitrothion exposure		
	NIW	NE	Any
GESTATION = 20-36 weeks			
- Cases	3	0	0
- Controls	27	18	7
- SRR	1.00	0.00	0.00
- Chi-square		0.58	0.01
- p-value		.4462	.9184
GESTATION = 37+ weeks			
- Cases	14	5	8
- Controls	437	175	106
- SRR	1.00	0.89	2.36
- Chi-square		0.00	2.75
- p-value		.9671	.0975
Summary Analysis			
- Mantel-Haenszel or	1.00	0.69	1.94
- Lower 95% limit		0.16	0.70
- Upper 95% limit		2.97	5.37

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F28.4

Risk of fenitrothion exposure in the first trimester window
in renal agenesis cases by maternal SJRB residential
status, all controls

Analysis	Fenitrothion exposure		
	NIW	NE	Any
<u>SJRB = NO</u>			
- Cases	7	2	3
- Controls	227	106	42
- SRR	1.00	0.61	2.32
- Chi-square		0.06	0.60
- p-value		0.8039	0.4381
<u>SJRB = YES</u>			
- Cases	10	3	5
- Controls	237	87	71
- SRR	1.00	0.82	1.67
- Chi-square		0.00	0.36
- p-value		0.9856	0.5458
<u>Summary Analysis</u>			
- Mantel-Haenszel OR	1.00	0.72	1.88
- Lower 95% limit		0.14	0.67
- Upper 95% limit		3.68	5.28

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F28.5

Risk of exposure to agricultural chemicals in the first trimester window in renal agenesis cases by maternal SJRB residential status, all controls

Analysis	Agricultural chemical exposure			
	NIW	NE	1-20	21+
<u>SJRB = NO</u>				
- Cases	2	0	3	7
- Controls	155	1	39	180
- SRR	1.00	0.00	5.96*	3.01
- Chi-square		19.00	2.56	1.18
- p-value		0.000	.1097	.2763
<u>SJRB = YES</u>				
- Cases	5	5	3	5
- Controls	138	95	37	125
- SRR	1.00	1.45	2.24	1.10
- Chi-square		0.06	0.43	0.03
- p-value		.8011	.5121	.8661
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	1.44	3.28	1.70
- Lower 95% limit		0.07	0.93	0.51
- Upper 95% limit		27.82	11.55	5.72

* SRR significant at $p \leq .05$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F28.6

Risk of agricultural chemical exposure in the first trimester window in renal agenesis cases by maternal north/south¹ residence, all controls

Analysis	Agricultural chemical exposure			
	NIW	NE	1-20	21+
<u>SOUTH</u>				
- Cases	2	5	1	8
- Controls	133	95	12	119
- SRR	1.00	3.50	5.54	4.47
- Chi-square		1.39	0.24	2.92
- p-value		.2387	.6272	.0876
<u>NORTH</u>				
- Cases	5	0	5	4
- Controls	160	1	64	186
- SRR	1.00	0.00*	2.50	0.69
- Chi-square		7.56	1.20	0.05
- p-value		.0060	.2725	.8304
<u>Summary Analysis</u>				
- Mantel-Haenszel OR	1.00	3.37	2.82	1.66
- Lower 95% limit		0.42	0.75	0.52
- Upper 95% limit		27.07	10.66	5.32

¹ Southern counties are 1-8, northern counties are 9-15.

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F29

Risk¹ of a Neural Tube Defect after Exposure to
Fenitrothion in the periconceptional window,
by control group

CONTROL GROUP	ANALYSIS	FENITROTHION EXPOSURE			
		NIW	NE	1-10	11+
1	Unadjusted	1.00	0.66	1.51	1.42
	20-36 weeks	1.00	0.39	1.08	2.16
	37-38 weeks	1.00	0.63	3.15	2.52
	39+ weeks	1.00	0.69	1.01	0.63
	Summary	1.00	0.60	1.43	1.17
2	Unadjusted	1.00	0.92	1.08	0.97
	20-36 weeks	1.00	2.08	0.96	1.92
	37-38 weeks	1.00	0.90	3.61	--2
	39+ weeks	1.00	0.84	0.65	0.36
	Summary	1.00	0.94	1.08	0.88

¹ Risk ratio standardized to the NIW category in each analysis.

² SRR cannot be calculated due to zero cells

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F30

Risk of a Neural Tube Defect After Exposure to Fenitrothion
spraying in the periconceptional window by SJRB
residential status, all controls

ANALYSIS	FENITROTHION EXPOSURE			
	NIW	NE	1-10	11+
Unadjusted				
Cases	161	37	12	13
SRR	1.00	0.77	1.26	1.15
p-Value		.2322	.6409	.8143
Residence = <u>SJRB = NO</u>				
Cases	81	17	2	6
SRR	1.00	0.70	2.18	0.73
p-Value		.2738	.7367	.6418
Residence = <u>SRJB = YES</u>				
Cases	80	20	10	7
SRR	1.00	0.85	1.18	2.18
p-Value		.6441	.8196	.1917
Summary				
M-H OR	1.00	0.77	1.29	1.15
p-Value		.2325	.6031	.8053

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F31

Risk of a Neural Tube Defect After Exposure to Fenitrothion
spraying in the periconceptional window by north/south
residential status, all controls

ANALYSIS	FENITROTHION EXPOSURE			
	NIW	NE	1-10	11+
Unadjusted				
Cases	161	37	12	13
SRR	1.00	0.77	1.26	1.15
p-Value		.2322	.6409	.8143
Residence = <u>SJRB</u> = NO				
Cases	61	16	5	1
SRR	1.00	0.88	1.62	0.35
p-Value		.7805	.5571	.4983
Residence = <u>SRJB</u> = YES				
Cases	100	21	7	12
SRR	1.00	0.70	1.04	1.30
p-Value		.2425	.8834	.5995
Summary				
M-H OR	1.00	0.77	1.23	1.05
p-Value		.2419	.6740	.9815

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F32

Risk of a Neural Tube Defect after Exposure to Agriculture
Chemical spraying in the periconceptional window, by
control group and gestational age category

CONTROL GROUP	ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE			
		NIW ^c	NE ^d	1-10	11+
1	Unadjusted	1.00	0.61	1.10	1.07
	Gestation (wks) 20-36		0.19*	0.92	0.75
	37-38		1.46	0.44	3.32*
	39-40		0.61	1.01	0.87
	41+		0.82	1.48	1.18
	Summary		0.60	0.97	1.15
2	Unadjusted	1.00	0.74	1.76	1.13
	Gestation (wks) 20-36		0.38	— ¹	0.85
	37-38		1.63	1.63	1.82
	39-40		0.74	1.33	1.13
	41+		0.78	3.53	1.00
	Summary		0.80	1.96	1.17

* SRR significant at $p \leq 0.05$

¹ SRR cannot be calculated

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE 33

Risk of a Neural Tube Defect After Exposure to Agricultural
Chemical spraying in the periconceptional window by
SJRJ residential status, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE			
	NIW	NE	1-20	21+
Unadjusted				
Cases	111	17	24	71
SRR	1.00	0.67	1.37	1.10
p-Value		.2104	.2933	.6267
Residence = <u>SJRJ</u> = NO				
Cases	53	2	11	40
SRR	1.00	7.85	1.35	1.17
p-Value		.2118	.5597	.5834
Residence = <u>SRJB</u> = YES				
Cases	58	15	13	31
SRR	1.00	0.54	1.37	1.06
p-Value		.0702	.4947	.9289
Summary				
M-H OR	1.00	0.64	1.36	1.12
p-Value		.1654	.3004	.5822

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F34

Risk of a Neural Tube Defect After Exposure to Agricultural
Chemical spraying in the periconceptional window by
north/south residential status, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE			
	NIW ^e	NE ^f	1-20	21+
Unadjusted				
Cases	111	17	24	71
SRR	1.00	0.67	2.83*	1.59*
p-Value		.2104	.001	.0124
Residence = SOUTH				
Cases	40	16	6	21
SRR	1.00	0.82	3.38	1.14
p-Value		.6429	.0572	.7798
Residence = NORTH				
Cases	71	1	18	50
SRR	1.00	2.99	2.44*	1.99*
p-Value		.9932	.0145	.0035
Summary				
M-H OR	1.00	0.87	2.65*	1.62*
p-Value		.7622	.001	.010

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F35

Risk of Anencephalus After Exposure to Fenitrothion in the periconceptional window by gestational age category, all controls

ANALYSIS	FENITROTHION EXPOSURE			
	NIW	NE	1-10	11+
Gestation = 20-36 wks				
Cases	37	11	3	4
Controls	34	14	2	2
SRR	1.00	0.72	1.38	1.84
Lower 95% limit		0.26	0.22	0.32
Upper 95% limit		1.98	8.81	10.58
Gestation = 37-38 wks				
Cases	10	0	2	1
Controls	73	18	4	2
SRR	1.00	0.00	3.65	3.65
Lower 95% limit		—	0.65	0.35
Upper 95% limit		--	20.61	38.42
Gestation = 39+ wks				
Cases	29	3	2	1
Controls	432	129	36	34
SRR	1.00	0.35	0.83	0.44
Lower 95% limit		0.11	0.19	0.06
Upper 95% limit		1.10	3.61	3.14
Summary				
M-H OR	1.00	0.45*	1.34	1.10
		0.21	0.26	0.19
		0.96	6.80	6.20

M-H Extension Chi-square: 0.166, 1 df., p = .6837

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE 36

Risk of Anencephalus After Exposure to Fenitrothion in the
periconceptual window by SJRB residence status,
all controls

ANALYSIS	FENITROTHION EXPOSURE			
	NIW	NE	1-10	11+
SRJB = NO				
Cases	39	6	1	2
Controls	265	80	3	27
SRR	1.00	0.51	2.26	0.50
Lower 95% limit		0.19	0.24	0.12
Upper 95% limit		1.32	21.09	2.15
SJRB = YES				
Cases	37	8	6	4
Controls	274	81	29	11
SRR	1.00	0.73	1.53	2.69
Lower 95% limit		0.30	0.53	0.68
Upper 95% limit		1.72	4.21	9.82
Summary				
M-H OR	1.00	0.62	1.61	1.12
Lower 95% limit		0.32	0.52	0.00
Upper 95% limit		1.18	4.99	99.99

M-H Extension Chi-square: .282, 1 df., p = .5952

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F37

Risk of Anencephalus After Exposure to Fenitrothion in the periconceptional window by north/south residential status, all controls

ANALYSIS	FENITROTHION EXPOSURE			
	NIW	NE	1-10	11+
Residence = SOUTH				
Cases	27	5	3	0
Controls	257	77	13	12
SRR	1.00	0.62	2.20	0.00
Lower 95% limit		0.20	0.61	--
Upper 95% limit		1.76	7.97	--
Residence = NORTH				
Cases	49	9	4	6
Controls	282	84	19	26
SRR	1.00	0.62	1.21	1.33
Lower 95% limit		0.27	0.33	0.46
Upper 95% limit		1.37	4.00	3.62
Summary				
M-H OR	1.00	0.62	1.51	1.01
Lower 95% limit		0.32	0.49	0.90
Upper 95% limit		1.18	4.71	1.14

M-H Extension Chi-square: .090, 1 df., p = .7645

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F38

Risk of Anencephalus After Exposure to Agricultural
Chemicals in the periconceptional window by gestational
age category, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE			
	NIW	NE	1-20	21+
Gestation = 20-36 wks				
Cases	30	2	9	14
Controls	24	10	4	14
SRR	1.00	0.16	1.80	0.80
Lower 95% limit		0.04	0.49	0.32
Upper 95% limit		0.71	6.56	2.01
Gestation = 37+ wks				
Cases	23	2	3	20
Controls	368	79	58	215
SRR	1.00	0.41	0.83	1.49
Lower 95% limit		0.10	0.24	0.80
Upper 95% limit		1.68	2.84	2.77
Summary				
M-H OR	1.00	0.27	1.19	1.22
Lower 95% limit		0.09	0.17	0.66
Upper 95% limit		0.82	8.17	2.26

M-H Extension Chi-square: 1.916, 1 df., p = .1663

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F39

Risk of Anencephalus After Exposure to Agricultural
Chemicals in the periconceptional window by SJRB
residential status, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE				
	NIW	NE	1-10	11-40	41+
SJRB = NO					
Cases	25	1	4	8	10
Controls	208	1	17	85	64
SRR	1.00	8.32	1.96	0.78	1.30
Lower 95% limit		0.79	0.51	0.31	0.55
Upper 95% limit		88.16	6.89	1.91	3.02
SJRB = YES					
Cases	28	3	2	15	7
Controls	184	88	0	97	26
SRR	1.00	0.22*	—	1.02	1.77
Lower 95% limit		0.07	—	0.49	0.63
Upper 95% limit		0.69	—	2.09	4.80
Summary					
M-H OR	1.00	0.33*	2.99	0.91	1.47
Lower 95% limit		0.11	0.97	0.39	0.74
Upper 95% limit		0.96	9.20	2.16	2.92

* SRR significant at p .05

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F40

Risk of Anencephalus After Exposure to Agricultural
Chemicals in the periconceptual window by north/south
residential status, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE			
	NIW	NE	1-20	21+
Residence = SOUTH				
Cases	18	4	3	10
Controls	180	88	8	83
SRR	1.00	0.45	3.75	1.20
Lower 95% limit		0.13	0.99	0.53
Upper 95% limit		1.48	14.18	2.72
Residence = NORTH				
Cases	35	0	9	24
Controls	212	1	54	144
SRR	1.00	0.00	1.01	1.01
Lower 95% limit		—	0.42	0.55
Upper 95% limit		—	2.35	1.83
Summary				
M-H OR	1.00	0.44	1.29	1.07
Lower 95% limit		0.12	0.52	0.48
Upper 95% limit		1.62	3.19	2.40

M-H Extension Chi-square: .333, 1 df., p = .5640

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F41

Risk of Spina Bifida With Hydrocephalus After Exposure
to Fenitrothion in the periconceptional window by
gestational age category, all controls

ANALYSIS	FENITROTHION EXPOSURE		
	NIW	NE	Any
Gestation = 20-36 wks			
Cases	7	4	1
Controls	107	32	10
SRR	1.00	1.91	1.53
Lower 95% limit		0.44	0.17
Upper 95% limit		7.93	13.62
Gestation = 37+ wks			
Cases	35	8	3
Controls	432	129	60
SRR	1.00	0.77	0.62
Lower 95% limit		0.32	0.19
Upper 95% limit		1.77	2.05
Summary			
M-H OR	1.00	0.96	0.73
Lower 95% limit		0.08	0.12
Upper 95% limit		11.16	4.31

M-H Extension Chi-square: .325, 1 df., p = .5686

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F42

Risk of Spina Bifida with Hydrocephalus after Exposure
to Fenitrothion in the periconceptional window by SJRB
residential status, all controls

ANALYSIS	FENITROTHION EXPOSURE		
	NIW	NE	Any
SJRB = NO			
Cases	19	7	3
Controls	265	80	30
SRR	1.00	1.22	1.39
Lower 95% limit		0.45	0.39
Upper 95% limit		3.21	4.97
SJRB = YES			
Cases	23	5	1
Controls	274	81	40
SRR	1.00	0.74	0.30
Lower 95% limit		0.24	0.04
Upper 95% limit		2.13	2.03
Summary			
M-H OR	1.00	0.96	0.73
Lower 95% limit		0.10	0.12
Upper 95% limit		8.74	4.40

M-H Extension Chi-square: .329, 1 df., p = .5664

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F43

Risk of Spina Bifida With Hydrocephalus After Exposure
to Fenitrothion in the periconceptual window by
north/south residential status, all controls

ANALYSIS	FENITROTHION EXPOSURE		
	NIW	NE	Any
Residence = SOUTH			
Cases	17	7	1
Controls	257	77	25
SRR	1.00	1.37	0.60
Lower 95% limit		0.50	0.08
Upper 95% limit		3.68	4.65
Residence = NORTH			
Cases	25	5	3
Controls	282	84	45
SRR	1.00	0.67	0.75
Lower 95% limit		0.22	0.22
Upper 95% limit		1.92	2.59
Summary			
M-H OR	1.00	0.96	0.71
Lower 95% limit		0.13	0.13
Upper 95% limit		6.87	3.80

M-H Extension Chi-square: .373, 1 df., p = .5415

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F44

Risk of Spina Bifida With Hydrocephalus After Exposure
to Agricultural Chemicals in the periconceptional
window by gestational age category, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE		
	NIW	NE	Any
Gestation = 20-36 wks			
Cases	5	2	5
Controls	78	21	50
SRR	1.00	1.49	1.56
Lower 95% limit		0.27	0.37
Upper 95% limit		8.20	6.63
Gestation = 37+ wks			
Cases	26	3	17
Controls	314	68	239
SRR	1.00	0.53	0.86
Lower 95% limit		0.16	0.43
Upper 95% limit		1.78	1.69
Summary			
M-H OR	1.00	0.71	0.96
Lower 95% limit		0.17	0.00
Upper 95% limit		3.03	308.50

M-H Extension Chi-square: .001, 1 df., p = .9808

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F45

Risk of Spina Bifida with Hydrocephalus after Exposure
to Agricultural Chemicals in the periconceptional
window by SJRB residential status, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE			
	NIW	NE	1-30	31+
SJRB = NO				
Cases	13	0	9	7
Controls	208	1	77	89
SRR	1.00	0.00	1.87	1.26
Lower 95% limit		—	0.70	0.44
Upper 95% limit		—	4.91	3.52
SJRB = YES				
Cases	18	5	4	2
Controls	184	88	85	38
SRR	1.00	0.58	0.48	0.54
Lower 95% limit		0.18	0.13	0.12
Upper 95% limit		1.73	1.57	2.37
Summary				
M-H OR	1.00	0.57	1.01	0.94
Lower 95% limit				
Upper 95% limit				

M-H Extension Chi-square: .021, 1 df., p = .8841

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F46

Risk of Spina Bifida With Hydrocephalus After Exposure
to Agricultural Chemicals in the periconceptual
window by north/south residential status, all controls

ANALYSIS	AGRICULTURAL CHEMICALS EXPOSURE		
	NIW	NE	Any
Residence = SOUTH			
Cases	13	5	7
Controls	179	88	91
SRR	1.00	0.78	1.06
Lower 95% limit		0.23	0.37
Upper 95% limit		2.46	2.97
Residence = NORTH			
Cases	18	0	15
Controls	212	1	198
SRR	1.00	0.00	0.89
Lower 95% limit		--	0.41
Upper 95% limit		--	1.92
Summary			
M-H OR	1.00	0.77	0.95
Lower 95% limit		0.08	0.06
Upper 95% limit		7.19	16.32

M-H Extension Chi-square: .010, 1 df., p = .9208

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F47

Risk of Spina Bifida Without Hydrocephalus After
Exposure to Fenitrothion in the periconceptional window
by gestational age category, all controls

ANALYSIS	FENITROTHION EXPOSURE		
	NIW	NE	Any
Gestation = 20-36 wks			
Cases	31	5	8
Controls	107	32	10
SRR	1.00	0.54	2.76
Lower 95% limit		0.17	0.90
Upper 95% limit		1.62	8.45
Gestation = 37+ wks			
Cases	21	8	1
Controls	432	129	60
SRR	1.00	1.28	0.34
Lower 95% limit		0.51	0.05
Upper 95% limit		3.12	2.37
Summary			
M-H OR	1.00	0.87	1.43
Lower 95% limit		0.31	0.45
Upper 95% limit		2.40	4.47

M-H Extension Chi-square: .704, 1 df., p = .4016

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F48

Risk of Spina Bifida without Hydrocephalus after
Exposure to Fenitrothion in the periconceptual window
by SJRB residential status, all controls

ANALYSIS	FENITROTHION EXPOSURE			
	NIW	NE	1-10	11+
SRJB = NO				
Cases	25	4	0	2
Controls	265	80	3	27
SRR	1.00	0.53	0.00	0.79
Lower 95% limit		0.18	—	0.18
Upper 95% limit		1.55	—	3.49
SJRB = YES				
Cases	27	9	4	3
Controls	274	81	29	11
SRR	1.00	1.13	1.40	2.77
Lower 95% limit		0.47	0.39	0.76
Upper 95% limit		2.63	4.61	10.03
Summary				
M-H OR	1.00	0.84	1.26	1.40
Lower 95% limit		0.35	0.02	0.27
Upper 95% limit		2.01	81.70	7.23

M-H Extension Chi-square: .645, 1 df., p = .4219

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F49

Risk of Spina Bifida Without Hydrocephalus After
Exposure to Fenitrothion in the periconceptional window
by north/south residential status, all controls

ANALYSIS	FENITROTHION EXPOSURE			
	NIW	NE	1-10	11+
Residence = SOUTH				
Cases	18	5	1	1
Controls	257	77	13	12
SRR	1.00	0.93	1.10	1.19
Lower 95% limit		0.29	0.14	0.15
Upper 95% limit		2.77	8.90	9.68
Residence = NORTH				
Cases	34	8	3	4
Controls	282	84	19	26
SRR	1.00	0.79	1.31	1.28
Lower 95% limit		0.32	0.37	0.36
Upper 95% limit		1.87	4.65	4.17
Summary				
M-H OR	1.00	0.84	1.25	1.26
Lower 95% limit		0.35	0.02	0.11
Upper 95% limit		2.04	87.10	13.75

M-H Extension Chi-square: .310, 1 df., p = .5778

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F50

Risk of Spina Bifida Without Hydrocephalus After Exposure
to Agricultural Chemicals in the periconceptual window
by gestational age category, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE			
	NIW	NE	1-40	41+
Gestation = 20-36 wks				
Cases	19	5	6	14
Controls	78	21	25	24
SRR	1.00	0.98	0.99	2.39
Lower 95% limit		0.28	0.31	0.97
Upper 95% limit		3.23	3.00	5.94
Gestation = 37+ wks				
Cases	14	3	10	3
Controls	314	68	173	66
SRR	1.00	0.99	1.30	1.02
Lower 95% limit		0.28	0.52	0.28
Upper 95% limit		3.54	3.18	3.65
Summary				
M-H OR	1.00	0.98	1.16	1.83
Lower 95% limit		0.80	0.42	0.86
Upper 95% limit		1.20	3.23	3.92

M-H Extension Chi-square: 3.404, 1 df., p = .0650

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F51

Risk of Spina Bifida Without Hydrocephalus after Exposure to
Agricultural Chemicals in the periconceptional window by SJRB
residential status, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE			
	NIW	NE	1-40	41+
SJRB = NO				
Cases	16	1	5	9
Controls	208	1	102	64
SRR	1.00	13.00	0.64	1.83
Lower 95% limit		1.44	0.20	0.71
Upper 95% limit		117.60	1.92	4.65
SJRB = YES				
Cases	17	7	11	8
Controls	184	88	97	26
SRR	1.00	0.86	1.23	3.33*
Lower 95% limit		0.31	0.51	1.18
Upper 95% limit		2.31	2.90	9.25
Summary				
M-H OR	1.00	1.03	0.94	2.36*
Lower 95% limit		0.73	0.01	1.22
Upper 95% limit		1.46	114.10	4.57

M-H Extension Chi-square: 6.597, 1 df., p = .0102

* SRR significant at $p \leq .05$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F52

Risk of Spina Bifida With Hydrocephalus After Exposure to
Agricultural Chemicals in the periconceptional window
by north/south residential status, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE			
	NIW	NE	1-40	41+
Residence = SOUTH				
Cases	10	7	1	7
Controls	179	88	25	66
SRR	1.00	1.42	0.72	1.90
Lower 95% limit		0.47	0.09	0.62
Upper 95% limit		4.23	5.81	5.70
Residence = NORTH				
Cases	23	1	15	10
Controls	212	1	174	24
SRR	1.00	9.22	0.79	3.84*
Lower 95% limit		0.90	0.38	1.50
Upper 95% limit		94.18	1.65	9.73
Summary				
M-H OR	1.00	1.66	0.79	2.77*
Lower 95% limit		0.50	0.34	1.42
Upper 95% limit		5.49	1.80	5.39

M-H Extension Chi-square: 5.539, 1df., $p = .0186$

* SRR significant at $p \leq .05$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F53

Risk of Spina Bifida Without Hydrocephalus After Exposure to
Agricultural Chemicals in the periconceptual window by
north/south residential status, Control Group 1

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE			
	NIW	NE	1-40	41+
Residence = SOUTH				
Cases	10	7	1	7
Controls	99	47	11	37
SRR	1.00	1.47	0.90	1.87
Lower 95% limit		0.47	0.10	0.59
Upper 95% limit		4.55	7.77	5.87
Residence = NORTH				
Cases	23	1	15	10
Controls	89	0	94	7
SRR	1.00	—	0.62	5.53*
Lower 95% limit		—	0.29	1.70
Upper 95% limit		—	1.33	18.40
Summary				
M-H OR	1.00	1.75	0.64	3.12*
Lower 95% limit		0.50	0.30	1.47
Upper 95% limit		6.08	1.39	6.59

M-H Extension Chi-square: 4.457, 1 df., p = .0348

* SRR significant at p $\leq$.05

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F54

Risk of Spina Bifida Without Hydrocephalus After Exposure to
Agricultural Chemicals in the periconceptional window by
north/south residential status, Control Group 2

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE			
	NIW	NE	1-40	41+
Residence = SOUTH				
Cases	10	7	1	7
Controls	81	41	14	29
SRR	1.00	1.38	0.58	1.96
Lower 95% limit		0.44	0.07	0.60
Upper 95% limit		4.32	4.81	6.27
Residence = NORTH				
Cases	23	1	15	10
Controls	123	1	80	17
SRR	1.00	5.35	1.00	3.15*
Lower 95% limit		0.43	0.47	1.17
Upper 95% limit		66.91	2.15	8.44
Summary				
M-H OR	1.00	1.58	0.94	2.55*
Lower 95% limit		0.42	0.00	1.24
Upper 95% limit		5.91	99.99	5.22

M-H Extension Chi-square: 5.136, 1 df., p = .0234

* SRR significant at $p \leq .05$

NOTE: Abbreviations are explained in the Compendium of Abbreviations (Page 123)

TABLE F55.1

Risk of Spina Bifida (Total) After Potential Exposure
to Fenitrothion By Gestational Age; All Controls

	NIW	NE	Any
36 weeks			
Cases (n)	38	9	9
Controls (n)	107	32	10
SRR	1.00	0.79	2.53
lower CL		0.32	0.86
upper CL		1.93	7.41
37 + weeks			
Cases (n)	56	16	4
Controls (n)	432	129	60
SRR	1.00	0.96	0.51
lower CL		0.51	0.18
upper CL		1.78	1.44
Summary M-H OR	1.00	0.90	1.07
lower CL		0.46	0.02
upper CL		1.73	54.65

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F55.2

Risk of Spina Bifida (Total) After Potential Exposure
to Fenitrothion By SJRB Strata; All Controls

	NIW	NE	Any
SJRB = NO			
Cases (n)	44	11	5
Controls (n)	265	80	30
SRR	1.00	0.83	1.00
lower CL		0.38	0.32
upper CL		1.75	2.91
SJRB = YES			
Cases (n)	50	14	8
Controls (n)	274	81	40
SRR	1.00	0.95	1.10
lower CL		0.50	0.48
upper CL		1.80	2.48
Summary M-H OR	1.00	0.89	1.06
lower CL		0.47	0.00
upper CL		1.67	99.9

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F55.3

Risk of Spina Bifida (Total) After Potential Exposure
to Fenitrothion By North-South Strata; All Controls

	NIW	NE	Any
South			
Cases (n)	35	12	3
Controls (n)	257	77	25
SRR	1.00	1.14	0.88
lower CL		0.53	0.25
upper CL		2.42	3.07
North			
Cases (n)	59	13	10
Controls (n)	282	84	45
SRR	1.00	0.70	1.06
lower CL		0.37	0.47
upper CL		1.47	2.34
Summary M-H OR	1.00	0.90	1.01
lower CL		0.47	0.88
upper CL		1.70	1.17

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F55.4

Risk of Spina Bifida (Total) After Potential Exposure
to Agricultural Chemicals (ACEO Index) by Gestational
Age; All Controls

	NIW	NE	Any
36 weeks			
Cases (n)	24	7	25
Controls (n)	78	21	49
SRR	1.00	1.08	1.66
lower CL		0.37	0.81
upper CL		3.12	3.40
37 + weeks			
Cases (n)	40	6	30
Controls (n)	314	68	239
SRR	1.00	0.69	0.99
lower CL		0.28	0.60
upper CL		1.69	1.63
Summary M-H OR	1.00	0.84	1.19
lower CL		0.33	0.76
upper CL		2.17	1.87

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F55.5

Risk of Spina Bifida (Total) After Potential Exposure
to Agricultural Chemicals (ACEO Index) by SJRB Strata
All Controls

	NIW	NE	Any
SJRB = NO			
Cases (n)	29	1	30
Controls (n)	208	1	166
SRR	1.00	7.17	1.30
lower CL		0.64	0.75
upper CL		79.92	2.25
SJRB = YES			
Cases (n)	35	12	25
Controls (n)	184	88	123
SRR	1.00	0.72	1.07
lower CL		0.33	0.59
upper CL		1.52	1.94
Summary M-H OR	1.00	0.80	1.18
lower CL		0.33	0.75
upper CL		1.94	1.84

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F55.6

Risk of Spina Bifida (Total) After Potential Exposure
to Agricultural Chemicals (ACEO Index) by North-South
Strata; All Controls

	NIW	NE	Any
South			
Cases (n)	23	12	15
Controls (n)	202	100	106
SRR	1.00	1.06	1.28
lower CL		0.47	0.60
upper CL		2.36	2.71
North			
Cases (n)	41	1	40
Controls (n)	212	1	198
SRR	1.00	5.17	1.04
lower CL		0.42	0.65
upper CL		63.88	1.68
Summary M-H OR	1.00	1.16	1.11
lower CL		0.31	0.69
upper CL		4.33	1.81

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F56.1

Risk of stillbirth after second trimester opportunity
for any potential exposure^a by maternal age group
all controls

ANALYSIS	ANY WINDOW		MATERNAL AGE
	NO	YES	
SRR Lower 95% limit Upper 95% limit	1.00	1.07 0.51 2.22	≤ 19
SRR, limits	1.00	1.65 0.97 2.79	20-24
SRR, limits	1.00	0.95 0.54 1.66	25-29
SRR, limits	1.00	1.44 0.57 3.62	30-34
SRR, limits	1.00	0.72 0.12 4.37	35-39
SRR, limits	1.00	2.10 0.24 18.43	40+
M-H OR Lower 95% limit Upper 95% limit	1.00	1.24 0.92 1.68	Adjusted for age

^aAny forest herbicide, forest insecticide or ACEO Index

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F56.2

Risk of stillbirth after second trimester opportunity
for any potential exposure^a by paternal age group
all controls

ANALYSIS	ANY WINDOW		PATERNAL AGE
	NO	YES	
SRR Lower 95% limit Upper 95% limit	1.00	1.11 0.21 6.01	≤ 19
SRR, limits	1.00	1.36 0.89 2.08	20-29
SRR, limits	1.00	1.19 0.63 2.23	30-39
SRR, limits	1.00	3.09 0.86 11.42	40+
M-H OR Lower 95% limit Upper 95% limit	1.00	1.38 1.00* 1.91	Adjusted for age

^aAny forest herbicide, forest insecticide or ACEO Index

*p .05

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F56.3

Risk of stillbirth after second trimester opportunity
for any potential exposure^a by a north-south
residence status; all controls

ANALYSIS	ANY WINDOW	
	NO	YES
Residence = South		
Cases	52	90
Controls	131	163
SRR	1.00	1.39
Lower 95% limits		0.90
Upper 95% limits		2.14
Residence = North		
Cases	60	96
Controls	129	179
SRR	1.00	1.15
Lower 95% limits		0.76
Upper 95% limits		1.74
Summary		
M-H OR	1.00	1.26
Lower 95% limits		0.94
Upper 95% limits		1.70

^a Any forest herbicide, forest insecticide or ACEO Index.

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F56.4

Risk of stillbirth after second trimester opportunity
for any potential exposure^a by SJRB
residence status; all controls

ANALYSIS	ANY WINDOW	
	NO	YES
SJRB = No		
Cases	64	109
Controls	148	98
SRR	1.00	1.27
Lower 95% limits		0.86
Upper 95% limits		1.89
SJRB = YES		
Cases	48	77
Controls	112	144
SRR	1.00	1.25
Lower 95% limits		0.79
Upper 95% limits		1.98
Summary		
M-H OR	1.00	1.26
Lower 95% limits		0.94
Upper 95% limits		1.70

^a Any forest herbicide, forest insecticide or ACEO Index.

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F57.1

Risk of stillbirth after second trimester opportunity
for forest herbicide potential exposure^a by maternal
age group; all controls

ANALYSIS	ANY WINDOW		MATERNAL AGE
	NO	YES	
SRR	1.00	1.53	≤ 19
Lower 95% limit		0.71	
Upper 95% limit		3.33	
SRR, limits	1.00	1.53 0.91 2.58	20-24
SRR, limits	1.00	0.84 0.47 1.51	25-29
SRR, limits	1.00	1.36 0.49 3.75	30-34
SRR, limits	1.00	0.24 0.05 1.11	35-39
SRR, limits	1.00	0.38 0.03 5.27	40+
M-H OR	1.00	1.12	Adjusted for age
Lower 95% limit		0.81	
Upper 95% limit		1.55	

^aPotential exposure in the forest herbicide spray season

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F57.2

Risk of stillbirth after second trimester opportunity
for forest herbicide potential exposure^a by paternal
age group; all controls

ANALYSIS	ANY WINDOW		PATERNAL AGE
	NO	YES	
SRR Lower 95% limit Upper 95% limit	1.00	1.07 0.15 7.79	≤ 19
SRR, limits	1.00	1.39 0.90 2.14	20-29
SRR, limits	1.00	0.82 0.44 1.52	30-39
SRR, limits	1.00	1.25 0.33 4.77	40+
M-H OR Lower 95% limit Upper 95% limit	1.00	1.17 0.82 1.65	Adjusted for age

^a Potential exposure in the forest herbicide spray season.

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F57.3

Risk of stillbirth after second trimester opportunity
for forest herbicide potential exposure by
^anorth-south residence status; all controls

ANALYSIS	ANY WINDOW	
	NO	YES
Residence = South		
Cases	93	49
Controls	205	89
SRR	1.00	1.21
Lower 95% limits		0.77
Upper 95% limits		1.90
Residence = North		
Cases	102	54
Controls	205	103
SRR	1.00	1.05
Lower 95% limits		0.69
Upper 95% limits		1.61
Summary		
M-H OR	1.00	1.13
Lower 95% limits		0.81
Upper 95% limits		1.56

^a Potential exposure in the forest herbicide spray season.

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F57.4

Risk of stillbirth after second trimester opportunity
for forest herbicide potential exposure by ^aSJRB
residence status; all controls

ANALYSIS	ANY WINDOW	
	NO	YES
SJRB = No		
Cases	113	60
Controls	169	100
SRR	1.00	0.90
Lower 95% limits		0.59
Upper 95% limits		1.36
SJRB = YES		
Cases	82	43
Controls	182	74
SRR	1.00	1.29
Lower 95% limits		0.80
Upper 95% limits		2.09
Summary		
M-H OR	1.00	1.05
Lower 95% limits		0.70
Upper 95% limits		1.56

^a Potential exposure in the forest herbicide spray season.

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F58.1

Risk of stillbirth after second trimester exposure opportunity in the forest insecticide spray window^a by maternal age group; all controls

ANALYSIS	ANY WINDOW		MATERNAL AGE
	NO	YES	
SRR Lower 95% limit Upper 95% limit	1.00	1.56 0.72 3.36	≤ 19
SRR, limits	1.00	1.21 0.72 2.03	20-24
SRR, limits	1.00	0.93 0.57 1.67	25-29
SRR, limits	1.00	1.59 0.52 4.45	30-34
SRR, limits	1.00	2.65 0.60 12.21	35-39
SRR, limits	1.00	1.20 0.1 13.66	40+
M-H OR Lower 95% limit Upper 95% limit	1.00	1.25 0.92 1.71	Adjusted for age

^aPotential exposure in the forest insecticide spray season.

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F58.2

Risk of stillbirth after second trimester exposure opportunity
in the forest insecticide spray window^a by paternal
age group; all controls

ANALYSIS	ANY WINDOW		PATERNAL AGE
	NO	YES	
SRR Lower 95% limit Upper 95% limit	1.00	1.22 0.22 6.90	< 19
SRR, limits	1.00	1.22 0.80 1.88	20-29
SRR, limits	1.00	1.52 0.81 2.86	30-39
SRR, limits	1.00	2.14 0.57 8.26	40+
M-H OR Lower 95% limit Upper 95% limit	1.00	1.36 0.98 1.89	Adjusted for age

^aPotential exposure in the forest insecticide spray season.

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F58.3

Risk of stillbirth after second trimester exposure
opportunity in the forest insecticide window
^aSJRB residence status; all controls

ANALYSIS	ANY WINDOW	
	NO	YES
SJRB = No		
Cases	103	70
Controls	234	112
SRR	1.00	1.42
Lower 95% limits		0.96
Upper 95% limits		2.11
SJRB = YES		
Cases	80	45
Controls	171	85
SRR	1.00	1.13
Lower 95% limits		0.70
Upper 95% limits		1.82
Summary		
M-H OR	1.00	1.29
Lower 95% limits		0.96
Upper 95% limits		1.75

^a Potential exposure in the forest insecticide spray season.

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE F58.4

Risk of stillbirth after second trimester exposure
opportunity in the forest insecticide window
^aNorth-south residence status; all controls

ANALYSIS	ANY WINDOW	
	NO	YES
Residence = South		
Cases	84	58
Controls	191	103
SRR	1.00	1.28
Lower 95% limits		0.83
Upper 95% limits		1.97
Residence = North		
Cases	99	57
Controls	214	94
SRR	1.00	1.31
Lower 95% limits		0.86
Upper 95% limits		2.01
Summary		
M-H OR	1.00	1.30
Lower 95% limits		0.96
Upper 95% limits		1.75

^a Potential exposure in the forest insecticide spray season.

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE 59.1

Risk of stillbirth after second trimester
opportunity for exposure to any amount of
fenitrothion by county of maternal residence
all controls

COUNTY	# STILLBIRTHS EXPOSED	SRR ^a
01	2	1.02
02	1	2.25
03	2	0.80
04	0	0.00
05	3	1.46
06	0	0.00
07	5	1.00
08	0	0.00
09	11	1.21
10	9	1.11
11	1	0.77
12	1	0.35
13	0	0.00
14	1	1.68
15	5	1.01

Overall crude risk: SRR = 1.04, 95% limits 0.68-1.59.

Risk adjusted for county: SRR = 1.01, 95% limits 0.83-1.23.

^a Standardized risk ratio for any fenitrothion exposure relative to
NIW and NE categories in each county.

Note: Abbreviations are explained in the Compendium of Abbreviations (page
123).

TABLE 59.2

Risk of stillbirth after second trimester opportunity
for exposure to fenitrothion by gestational age groups,
all controls

GESTATIONAL AGE GROUP	FENITROTHION EXPOSURE OPPORTUNITY INDEX			
	NIW	NE	1-10	11+
36 weeks				
cases	77	36	16	14
controls	16	5	1	4
SRR	1.00	1.50	3.32	0.73
Lower 95% limit		0.46	0.45	0.19
Upper 95% limit		5.10	24.37	3.02
37 weeks				
cases	105	39	3	8
controls	387	114	33	42
SRR	1.00	1.26	0.34	0.70
Lower 95% limit		0.81	0.11	0.29
Upper 95% limit		1.96	1.06	1.61
M-H OR	1.00	1.29	0.62	0.71
Lower 95% limit		0.84	0.20	0.32
Upper 95% limit		1.98	1.92	1.56

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE 59.3

Risk of stillbirth after second trimester opportunity
for exposure to fenitrothion by selected maternal
age groups, all controls

ANALYSIS	FENITROTHION EXPOSURE OPPORTUNITY INDEX			
	NIW	NE	1-10	11+
Maternal age 19				
cases	35	12	6	4
controls	60	14	7	6
SRR	1.00	1.47	1.47	1.14
Lower 95% limit		0.56	0.40	0.25
Upper 95% limit		3.85	5.39	5.02
20-24				
cases	59	25	7	6
controls	160	45	16	22
SRR	1.00	1.51	1.19	0.74
Lower 95% limit		0.82	0.42	0.25
Upper 95% limit		2.78	3.27	2.05
25-29				
cases	57	20	2	7
controls	111	38	7	14
SRR	1.00	1.02	0.56	0.97
Lower 95% limit		0.52	0.11	0.33
Upper 95% limit		2.01	2.72	2.77
30+				
cases	31	18	4	5
controls	72	22	4	4
SRR	1.00	1.90	2.32	2.90
Lower 95% limit		0.84	0.45	0.62
Upper 95% limit		4.31	12.02	14.04
M-H OR	1.00	1.40	1.24	1.07
Lower 95% limit		0.98	0.58	0.32
Upper 95% limit		2.00	2.65	3.55

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE 59.4

Risk of stillbirth after second trimester opportunity
for exposure to fenitrothion by selected paternal
age groups, all controls

ANALYSIS	FENITROTHION EXPOSURE OPPORTUNITY INDEX			
	NIW	NE	1-10	11+
Paternal age $\leq$ 19				
cases	7	1	3	1
controls	12	2	2	3
SRR	1.00	0.86	2.57	0.57
Lower 95% limit		0.06	0.34	0.05
Upper 95% limit		11.94	19.45	6.83
Paternal age 20-29				
cases	86	32	10	10
controls	240	65	24	31
SRR	1.00	1.37	1.16	0.90
Lower 95% limit		0.82	0.50	0.39
Upper 95% limit		2.30	2.67	2.01
Paternal age 30+				
cases	45	28	5	6
controls	126	39	8	6
SRR	1.00	2.01	1.75	2.80
Lower 95% limit		1.06*	0.47	0.75
Upper 95% limit		3.79	6.32	10.46
M-H OR	1.00	1.58	1.40	1.16
Lower 95% limit		1.07*	0.68	0.48
Upper 95% limit		2.33	2.88	2.81

*p $\leq$.05

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE 59.5

Risk of stillbirth after second trimester opportunity
for exposure to fenitrothion by north-south residence
status, all controls

ANALYSIS	FENITROTHION EXPOSURE OPPORTUNITY INDEX			
	NIW	NE	1-10	11+
Residence = South				
cases	84	45	8	5
controls	189	71	19	15
SRR	1.00	1.43	0.95	0.75
Lower 95% limit		0.88	0.36	0.23
Upper 95% limit		2.30	2.40	2.30
Residence = North				
cases	98	30	11	17
controls	214	48	15	31
SRR	1.00	1.36	1.60	1.20
Lower 95% limit		0.79	0.66	0.60
Upper 95% limit		2.36	3.86	2.37
Summary M-H OR	1.00	1.40	1.24	1.05
Lower 95% limit		0.98	0.59	0.03
Upper 95% limit		2.00	2.62	34.87

M-H Extension chi-square: 0.023, 1df, p=.8794

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE 59.6

Risk of stillbirth after second trimester opportunity
for exposure to fenitrothion by SJRB residence
status, all controls

ANALYSIS	FENITROTHION EXPOSURE OPPORTUNITY INDEX			
	NIW	NE	1-10	11+
SJRB = No				
cases	103	47	5	18
controls	232	74	5	35
SRR	1.00	1.43	2.25	1.16
Lower 95% limit		0.91	0.55	0.60
Upper 95% limit		2.26	9.20	2.23
SJRB = Yes				
cases	79	28	14	4
controls	171	45	19	11
SRR	1.00	1.35	1.59	0.79
Lower 95% limit		0.76	0.71	0.20
Upper 95% limit		2.40	3.54	2.79
Summary M-H OR	1.00	1.40	1.74	1.06
Lower 95% limit		0.98	0.86	0.23
Upper 95% limit		1.99	3.51	4.94

M-H Extension chi-square: 0.153, 1df, p=.6957

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE 60.1

Risk of stillbirth after second trimester
opportunity for exposure to any amount of
agricultural chemical spray by county of
maternal residence, all controls

COUNTY	# STILLBIRTHS EXPOSED	SRR ^a
01	0	- ^b
02	2	0.62
03	4	0.42
04	0	0.00
05	5	4.63
06	2	0.57
07	34	1.91
08	6	0.86
09	22	1.14
10	16	0.76
11	4	0.56
12	8	2.25
13	4	2.10
14	6	0.95
15	27	1.29

Overall crude risk: SRR = 1.19, 95% limits 0.89-1.58.

Risk adjusted for county: SRR = 1.19, 95% limits 0.86-1.64.

^a Standardized risk ratio for any fenitrothion exposure relative to
NIW and NE categories in each county.

^b SRR cannot be calculated due to zero cells.

Note: Abbreviations are explained in the Compendium of Abbreviations (page
123).

TABLE 60.2

Risk of stillbirth after second trimester opportunity
for exposure to agricultural chemicals by selected
maternal age groups, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE OPPORTUNITY INDEX				
	NIW	NE	1-20	21-40	41+
Maternal age ≤ 19					
cases	27	8	4	10	8
controls	41	11	5	18	12
SRR	1.00	1.10	1.21	0.84	1.01
Lower 95% limit		0.35	0.24	0.31	0.32
Upper 95% limit		3.47	5.89	2.30	3.12
Maternal age 20-29					
cases	78	18	11	36	40
controls	195	41	31	86	60
SRR	1.00	1.10	0.89	1.05	1.67
Lower 95% limit		0.57	0.40	0.64	1.00*
Upper 95% limit		2.11	1.95	1.72	2.76
Maternal age 30+					
cases	22	5	6	17	8
controls	47	9	12	11	11
SRR	1.00	1.19	1.07	3.30	1.55
Lower 95% limit		0.30	0.31	1.21*	0.48
Upper 95% limit		4.53	3.62	9.12	4.95
M-H OR	1.00	1.11	0.98	1.23	1.52
Lower 95% limit		0.56	0.47	0.82	1.00*
Upper 95% limit		2.20	2.04	1.86	2.32

M-H Extension chi-square: 4.537, 1 df, p=0.332

*p $\leq$.05

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE 60.3

Risk of stillbirth after second trimester opportunity
for exposure to agricultural chemicals by selected
paternal age groups, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE OPPORTUNITY INDEX				
	NIW	NE	1-20	21-40	41+
Father's age $\leq$ 29					
cases	68	13	12	30	29
controls	1.83	39	24	78	55
SRR	1.00	0.90	1.35	1.04	1.42
Lower 95% limit		0.43	0.60	0.61	0.81
Upper 95% limit		1.87	3.00	1.77	2.49
Father's age $\leq$ 30					
cases	37	8	7	28	14
controls	80	19	21	38	21
SRR	1.00	0.91	0.72	1.59	1.44
Lower 95% limit		0.33	0.25	0.81	0.61
Upper 95% limit		2.46	2.00	3.12	3.37
M-H OR	1.00	0.90	1.04	1.23	1.43
Lower 95% limit		0.37	0.00	0.79	0.89
Upper 95% limit		2.17	99.99	1.89	2.29

M-H Extension chi-square: 3.539, 1df, $p=0.0599$

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE 60.4

Risk of stillbirth after second trimester opportunity
for exposure to agricultural chemicals by gestational
age groups, all controls

GESTATIONAL AGE GROUP	AGRICULTURAL CHEMICAL EXPOSURE OPPORTUNITY INDEX				
	NIW	NE	1-10	11+	41+
36 weeks					
cases	55	21	7	29	31
controls	12	2	3	5	4
SRR	1.00	2.29	0.51	1.27	1.69
Lower 95% limit		0.48	0.12	0.36	0.45
Upper 95% limit		10.83	2.23	4.61	6.85
37+ weeks					
cases	72	10	14	34	25
controls	271	59	46	119	73
SRR	1.00	0.64	1.15	1.08	1.29
Lower 95% limit		0.29	0.57	0.66	0.74
Upper 95% limit		1.37	2.29	1.75	2.24
M-H OR	1.00	0.81	1.01	1.10	1.35
Lower 95% limit		0.35	0.80	0.62	0.79
Upper 95% limit		1.86	1.29	1.94	2.30

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE 60.5

Risk of stillbirth after second trimester opportunity
for exposure to agricultural chemicals by
north-south residence status, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE OPPORTUNITY INDEX				
	NIW	NE	1-20	21-40	41+
Residence = South					
cases	59	30	2	4	47
controls	142	61	9	15	67
SRR	1.00	1.18	0.53	0.64	1.69
Lower 95% limit		0.67	0.11	0.17	1.01*
Upper 95% limit		2.08	2.50	2.19	2.81
Residence = North					
cases	68	1	19	59	9
controls	141	0	40	109	18
SRR	1.00	- ^a	0.98	1.12	1.04
Lower 95% limit		-	0.51	0.71	0.41
Upper 95% limit		-	1.91	1.76	2.60
Summary M-H OR	1.00	1.24	0.90	1.04	1.50
Lower 95% limit		0.66	0.36	0.45	0.96
Upper 95% limit		2.33	2.26	2.39	2.33

M-H Extension chi-square: 2.945, 1df, p=.0861

^a cannot be calculated due to zero cells

* p ≤ .05

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).

TABLE 60.6

Risk of stillbirth after second trimester opportunity
for exposure to agricultural chemicals by SJRB
residence status, all controls

ANALYSIS	AGRICULTURAL CHEMICAL EXPOSURE OPPORTUNITY INDEX					
	NIW	NE	1-20	21-30	31-40	41+
SJRB = No						
cases	71	3	15	25	13	46
controls	164	5	35	47	26	69
SRR	1.00	1.39	0.99	1.23	1.15	1.54
Lower 95% limit		0.32	0.48	0.68	0.53	0.94
Upper 95% limit		5.94	2.02	2.23	2.51	2.52
SJRB = Yes						
cases	56	28	6	21	4	10
controls	119	56	14	44	7	16
SRR	1.00	1.06	0.91	1.01	1.21	1.33
Lower 95% limit		0.59	0.29	0.53	0.28	0.52
Upper 95% limit		1.92	2.71	1.94	4.88	3.35
Summary M-H OR	1.00	1.10	0.96	1.12	1.17	1.49
Lower 95% limit		0.48	0.01	0.68	0.46	0.97
Upper 95% limit		2.53	102.41	1.87	3.00	2.29

M-H Extension chi-square: 3.090, 1df, p=.0788

Note: Abbreviations are explained in the Compendium of Abbreviations (page 123).